

In late 2016-early 2017, the DMR will incorporate and support the Google cloud genomics infrastructure currently being used by the PDGSC for exome meta analysis. Migration of the DMR repository to a Cloud based storage system will enable WGS data to be stored when available. To manage data access to exome and WGS data, the DMR repository will link clinical, biomarker or other data types to individual level genomic data files in the Cloud. For the summary exome and whole genome variant data, a searchable file on the public PDBP website will be provided.

PD AMP Knowledge Platform: To customize AMP-PD data access, a public AMP-PD website will be established to direct users to appropriate raw and processed data. The public site will have a searchable aggregate file of human variant and expression data that is updated weekly and includes information on the analysis pipeline and quality control measures used to generate the aggregated data. The public site will also provide information about AMP-PD, a timeline for data releases, a catalog of datasets available with dataset statistics and a link to the controlled access database. Links to data analysis tools will be available through the public site and as a tools module in the DMR. Publications, presentations and news, will be available on the public site. Additional support will be required to process raw data through the established analytical pipelines.

Data Analysis: Standardized data analysis pipelines will be developed for WGS, RNA seq, epigenomics, and proteomics data types regardless of the AMP-PD platform used. An AMP-PD data analysis committee made up of industry and academic investigators will determine the standard data analysis pipelines to be used by AMP-PD. Since many data analysis pipeline currently exist through NIH (LINCS, NeuroLINCS, exRNA Atlas, GTEx, Epigenome Atlas) and other sponsored programs, it is anticipated that existing solutions for many of the data types to be collected in the AMP-PD project will be available. Further support and development will be required for data integration tools and machine learning tools for robotic microscopy.

Research design:

Several platforms meet the criteria of high-throughput, precision, and genome-scale resolution and can be considered for prioritization. Regardless of the platform/analytes and imaging modalities that are ultimately prioritized, resulting data should be made publicly accessible in real time, through easily accessible data dumps.

Specifically, this proposal will seek to generate data and promote analyses to answer two broad research questions:

1. Develop predictive models based on clinical, genetic, molecular and imaging profiles that relate early changes in these profiles to long-term disease prognosis.
2. Determine a molecular profile and imaging signature that defines specific genetic forms of PD (GBA and LRRK2) and determine whether this profile identifies subsets of idiopathic PD.

Deep molecular profiling:

For this proposal, a wide variety of platforms can be considered; and the list below shows possible technologies for identification of biomarkers. While these technologies cover many widely different aspects of whole-organism physiology, it is important to note that they are not limited by the analytes which will be assays, i.e., they are all open platforms. While hypothesis-based biomarker identification studies have had some success in PD, they have failed to establish disease progression markers that would be of utility to individual patients or in clinical trials. For this reason, open platforms will be prioritized over hypothesis-based research for the various -omics studies. The list given below is not meant to be comprehensive, and investigators may use one or more of the listed technologies, or may suggest other platforms, assuming that they have been fully validated. Note that in all cases the selection of the final platform will require the definition of, and performance against defined criteria for reproducibility and precision of measurement.

1. **Proteomics:** CSF will be of high interest, although other sample types will not be ruled out at this point. Multiple well-established platforms are available, and these may be run by the investigator (e.g., mass spectrometry, protein chips) or may be outsourced to proteomic vendors (e.g., Somalogics, MSBioworks, etc.). If multiple investigators/sites are performing proteomic analysis, alignment of measurement will be necessary through some method such as standardized samples, shared serial dilutions for calibration, etc.
2. **Transcriptomics:** RNA sequencing will primarily utilize blood samples from Paxgene tubes. RNAseq has many advantages over microarrays, including transcriptome-wide and splice variant coverage, precision, high throughput,

high resolution for isoforms, genome-scale coverage, ability to discover of novel disease-linked transcripts, as well as non-coding transcripts (e.g., microRNAs).

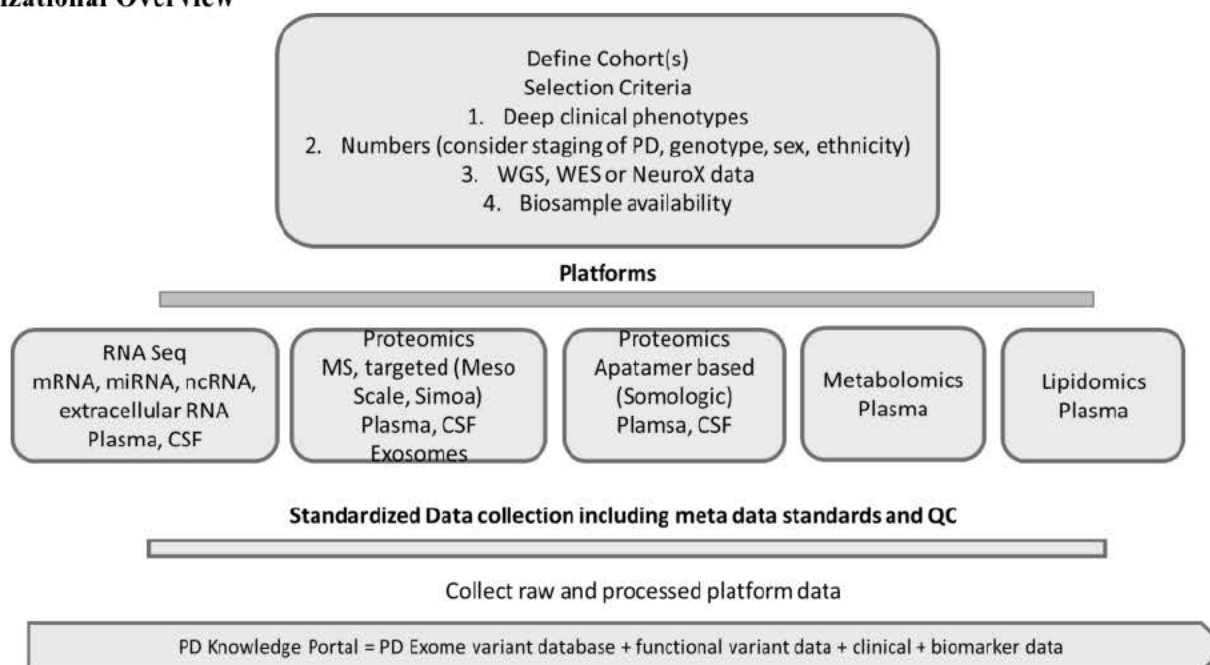
3. **Metabolomics:** While a high percentage of the biomarker work to date has focused on proteomics and transcriptomics, a great deal of both organism- and cellular-level physiology is missed by these platforms. Metabolomics studies the end products of cellular processes and enzymatic reactions, which may often track more dynamic changes in physiology than can be measured by protein or RNA levels. A wide-range of samples could be used (CSF, plasma, urine).

4. **Lipidomics:** This methodology will be of high interest in sporadic cases, but especially in GBA-associated PD. Dysregulated glucosylceramides likely include more than just glucosylceramide and glucosylsphingosine, and an open-platform analysis of lipids can establish a more complete picture of changes, as well as establishing if any are sufficiently dynamic as to function as markers of disease progression or state.

Imaging Signatures

Numerous imaging modalities now exist from sources for biomarker development. These include PPMI, PDBP, ADNI, and others. Current PD studies with available data have focused on dopaminergic imaging and extensive data has demonstrated that dopamine transporter and to a lesser extent vesicular transporter imaging may be utilized as a clinical trials enrichment tool for stratification, as a tool to assess disease progression and as a tool for identification dopaminergic pathology prior to symptom onset in prodromal subjects. PET imaging targeting amyloid and tau also provide some opportunities to assess PD pathology and PD subsets though these data are less available in current cohorts. Other promising scintigraphic imaging tools include markers for inflammation, specific striatal or brainstem dysfunction (adenosine, glutamate, PDE10, serotonin, etc.), and focused genetic markers (LRRK2, GBA, Synuclein) but would require acquisition of data. MRI measures including diffusion weighted imaging using a free-water imaging or other multi-tensor analytical approach, structural imaging to assess cortical and subcortical volume, structural imaging to measure cortical thinning, and resting state functional MRI have also shown great promise. Each of these modalities are available in the public databases for validation and new biomarker discovery. Other modalities are not readily available in PPMI, but may be available in PDBP include susceptibility weighted imaging. New biomarker discovery would focus on new analytical approaches to the already available imaging modalities. A key area for further data mining would be to assess how an imaging modality relates to genetic polymorphisms or how an imaging modality relates to alpha-synuclein accumulation or other biofluid assays. Developing reliable progression markers that track key areas of interest in PD are of high interest, as are predictors of future motor and cognitive decline. Further, combining imaging modalities for multi-modal imaging may offer critical insights in the same way that hippocampal volume and amyloid imaging have in the area of AD.

Organizational Overview



Cohorts

Priority should be given to use of samples that address the research questions outlined above.

To address question #1, studies will require samples from longitudinal cohorts that have well characterized longitudinal clinical and imaging data to stratify the cohorts at baseline and to identify and assess subsets of disease progression to determine and ultimately predict long-term prognosis based on biomarker signature. Treatment of PD subjects is inevitable, but creates a major confound in longitudinal PD studies. Therefore, biomarker assessment should address the effect of PD medications. Priority should be given to samples within the first year of disease to enhance the number of subjects still untreated. Samples from the PPMI study may be most suited for this analysis. Cohorts such as PPMI and PARS with prodromal subjects may offers the opportunity for longer biomarker follow-up without medication confound.

To address question #2, studies should utilize samples from genetic populations including PPMI, PDBP, LCC (LRRK2 cohort consortium) and the Harvard Biomarkers Study (HBS) as well as samples from idiopathic PD populations including PPMI, PDBP, BioFind, and Harvard Biomarkers Study.

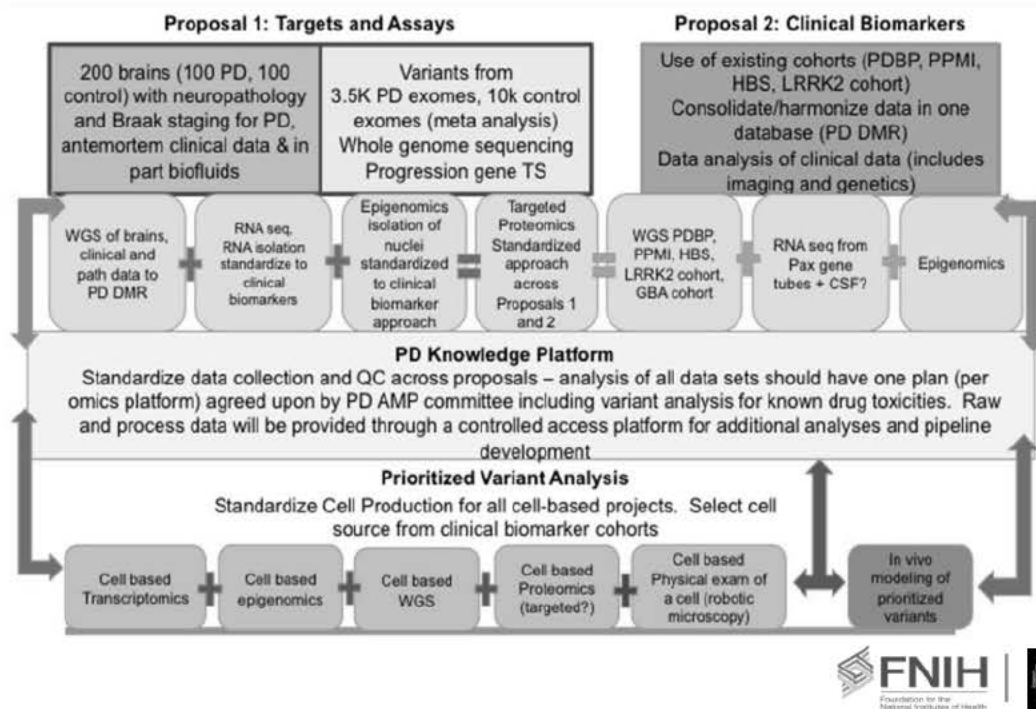
The recommendation is to conduct discovery work on as many samples as possible to allow flexibility in analytic approaches and to maximize sample sizes and replication opportunities.

| Cohort | DNA | RNA | CSF | Whole blood | Blood Pellet | Plasma | Serum | Urine | Saliva | Cell Lines | PBMCs |
|--|-----|-----|-----|-------------|--------------|--------|-------|-------|--------|------------|-------|
| PPMI | ✓ | ✓ | ✓ | ✓ | | ✓ | ✓ | ✓ | | ✓ | ✓ |
| BioFIND | ✓ | ✓ | ✓ | | ✓ | ✓ | | ✓ | ✓ | | |
| PDBP | ✓ | ✓ | ✓ | ✓ | | ✓ | ✓ | | | | ✓ |
| LCC | | ✓ | ✓ | ✓ | | ✓ | ✓ | ✓ | | | |
| 24-Hour Biofluid Sampling | | | ✓ | ✓ | | ✓ | ✓ | | | | |
| DATATOP | ✓ | | ✓ | | | | ✓ | ✓ | | | |
| Interventional Trials (SURE-PD, FS-Zone) | | ✓ | ✓ | ✓ | | ✓ | | ✓ | | | |
| LRRK2 Biobanking Initiative | | | | | | | | ✓ | | | ✓ |
| Harvard Biomarker Study | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | | | ✓ | ✓ |
| Kassel Repository | ✓ | ✓ | ✓ | ✓ | | ✓ | ✓ | ✓ | ✓ | | |

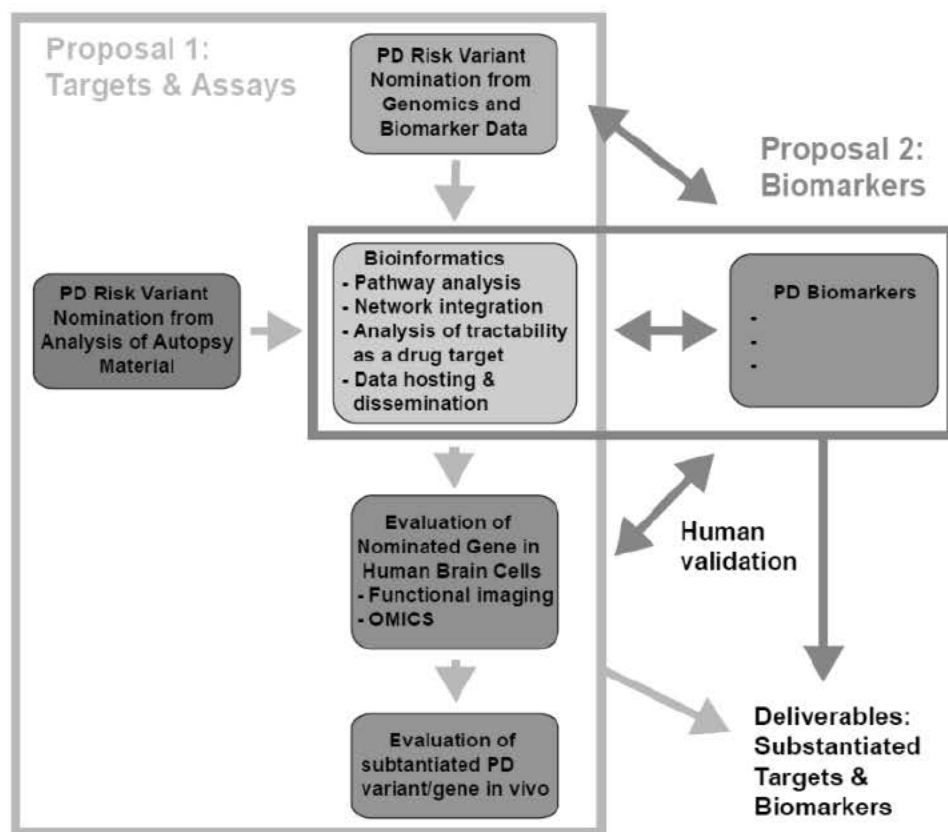
Deliverables:

1. Provide widely available dataset to allow analysis of PD subtypes and progression modeling.
2. Develop molecular profile models of genetic disease and how they relate to idiopathic PD.
3. Develop molecular models to predict PD progression.
4. Integrate molecular profiling data with existing neuroimaging and clinical data to establish relevant disease models.

PROPOSALS 1 & 2: SUMMARY, SYNERGIES, AND INTERACTIONS



Summary. Inspired by breakthrough genetics AMP-PD will enable tailored drugs --- by providing targets and assays --- and biomarkers for proof-of-concept trials. The three Platform analyses comprising the two AMP-PD Proposals – Human Functional Evaluation Platform, Human Brain Cell Platform, and Clinical Biomarkers Platform --- are highly complementary, synergistic, and integrated. Human disease biology will be probed in three human tissues: in patient-derived iPSCs, in patients’ brain cells, and in patients’ biofluids providing a layered, multi-dimensional view. Each level will add independent information on mechanism, on correlations with human neuropathology, and on the feasibility of tracking processes with biomarkers. Cross-cutting assay platforms – whole genome sequencing, transcriptomics, and epigenomics - will be used to probe each of the three human tissues thereby facilitating multi-scale integration in the AMP-PD Knowledge Platform. AMP-PD will build on extensive existing assets including breakthrough human genetics, existing iPSC lines of familial PD mutations, existing RNA-seq data from laser-captured nigral dopamine neurons, and extensive longitudinal clinical biofluid banks with linked longitudinal clinical phenotypes.



Synergies and interactions. The two proposals are deeply linked at the level of 1) identifying causal genetic variants, 2) identifying molecules and networks linked to genetics and α -synuclein pathology, 3) identifying and validating biomarkers of disease mechanism and progression.

The two Proposals will feed into each other (in both directions), and will mutually confirm results and in combination optimize the rankings of identified actionable targets for drug development.

Readouts from the iPSC work, which are found to change in response to genetic perturbation can be examined in nigral dopamine neurons, compared to Lewy body stages, and evaluated in the longitudinal biobank cohorts. The Brain Cell Platform can identify putative causal GWAS variants and their regulated

neuronal targets, which can be mechanistically tested on the iPSC platform and peripherally tracked with biomarkers highlighted in the Clinical Biomarkers Platform. Disease drivers and networks identified in human brains and human iPSCs will allow the identification of patients with matching molecular pathways in Proposal 2. This will potentially allow to identify PD subtypes with a unique genetic, molecular, clinical and imaging phenotype linked to a specific target mechanisms (from Proposal 1) and with linked tailored biomarkers (from 2). Such as specific PD subtype can then be used to inform enrollment or stratification of tailored POC trials.

Moreover, biomarkers found in open-platform screening of PD CSF or blood can be included as readout in the iPSC work and nigral dopamine neuron work to determine if any genetic variants affect its levels. Moreover, biomarkers can be examined for correlation with neuropathological Lewy body Braak stages in human brains. In this way, we may form a more complete picture of PD, from genetic variant through physiology to POC trials.

PROPOSED BUDGET AMP-PD

PROPOSAL 1 BUDGET ESTIMATE:

| PROPOSAL 1 | TOTAL w/o Buy Up | Total w/Buy Up phase 1 | Total w/Buy Up phase 2 | Total with All Buy Ups |
|--|------------------|------------------------|------------------------|------------------------|
| | (b) (4) | | | |
| Total Phase 0 | | | | |
| Total Phase 1 | | | | |
| Total Phase 2 | | | | |
| PD AMP portal and Integrative Bioinformatics | | | | |
| Total platform Costs | | | | |
| FNIH project/program management | | | | |
| Total Proposal 1 (W/O BUY UP OPTIONS) | | | | |
| BUY UP Option for Phase 1 | | | | |
| Total Proposal 1 (W/Ph1 BUY UP) | | | | |
| BUY UP Option for Phase 2 | | | | |
| TOTAL PROPOSAL 1 | | | | |

PROPOSAL 2 BUDGET ESTIMATE:

| PROPOSAL 2 | | TOTAL BASELINE ASSAYS + BUY UPS | TOTAL BASELINE + LONGITUDINAL ASSAYS | TOTAL BASELINE + LONGITUDINAL ASSAYS + ONLY BASELINE BUY UP | TOTAL BASELINE + LONGITUDINAL ASSAYS + ONLY LONGITUDINAL BUY UP | TOTAL BASELINE + LONGITUDINAL ASSAYS + ALL BUY UPS (BASELINE AND LONGITUDINAL) |
|--|---------|---------------------------------|--------------------------------------|---|---|--|
| DISCOVERY BASELINE | (b) (4) | | | | | |
| DISCOVERY REPLICATION | | | | | | |
| Personnel Costs | | | | | | |
| FNIH project/program management | | | | | | |
| TOTAL BASELINE (W/O BUY UP) | | | | | | |
| BUY UP for BASELINE ASSAYS | | | | | | |
| "total CSF Buy Up" | | | | | | |
| "total Plasma Buy Up" | | | | | | |
| "total CSF and Plasma Buy Up" (Baseline) | | | | | | |
| LONGITUDINAL (12months) BUY UP | | | | | | |
| Discovery (longitudinal assays) | | | | | | |
| Replication (longitudinal assays) | | | | | | |
| Total LONGITUDINAL BUY UP PROPOSAL | | | | | | |
| BUY UP for LONGITUDINAL ASSAYS | | | | | | |
| "total CSF Buy Up" | | | | | | |
| "total Plasma Buy Up" | | | | | | |
| "total CSF and Plasma Buy Up" (Longitudinal) | | | | | | |

Budget Justification

Proposal 1 Budget Explanation:

Phase 0 costs include: Genetic data analysis computational costs, cell source and differentiation protocol optimization for Phase 1 iPSC-based OMICS and *Human Functional Evaluation Platform* studies, immunohistochemical confirmation of PD and control brains to be used in the *Human Cell Platform* and related *AMP-PD Knowledge Platform* costs.

Phase 1 costs include: Human Functional Evaluation Platform costs such as cell differentiation and scale-up, OMICS analyses of transcriptome, epigenome, proteome and metabolome of cells with known disease-causing mutations and isogenic controls, and genetic manipulation of genes associated with variants identified and prioritized through PD genetic data analysis of GWAS, exome sequencing, whole genome sequencing and targeted sequencing data, as well as variants identified through the Human Cell and Clinical Biomarker Platforms. Costs also include the use of chemical or genetic perturbants to test the functional effects of prioritized pathways identified through integrative data analysis.

Phase 2 costs include: Further analysis of up to 50 targets and pathways identified and characterized by the Human Functional Evaluation platform, Human Cell platform and Clinical Biomarkers platform in appropriate *in vivo* model systems. Current cost analysis is based on the use of a rodent model system.

Buy Up Option costs for Phase 1 include: Analysis of the phosphoproteome using the P100 assay for OMICS studies, additional perturbant assessments using OMICS and robotic microscopy assays and unbiased proteomic analysis for the *Human Brain Cell Platform*.

Buy Up Option costs for Phase 2 include: Analysis of phosphoproteome using the P100 assay and global chromatin profiling.

Proposal 2 Budget Explanation:

Discovery baseline costs include: Analysis of PDBP, BioFIND and HBS RNA samples at baseline using RNA seq, unbiased proteome, metabolome and lipidomic analyses of PDBP, BioFIND and HBS CSF samples at baseline, epigenomic analysis (cell based) of PDBP, BioFIND and HSB samples at baseline.

Replication baseline costs include: Analysis of PPMI RNA samples at baseline using RNA seq, unbiased proteome, metabolome and lipidomic analysis of PPMI baseline CSF samples, epigenomic analysis (cell based) of PPMI baseline samples.

Buy up for Baseline assays total CSF: Include exRNA seq or exosome analysis of CSF at baseline from PDBP, HBS, BioFIND.

Buy up for Baseline assays total plasma: Include Somalogic or other unbiased proteomic, metabolomics or lipidomic analysis platform of plasma samples at baseline from PDBP, HBS and BioFIND.

Longitudinal (12 months) Buy up options:

Discovery costs for longitudinal follow up assays: Analysis of PDBP, BioFIND and HBS RNA samples at 12 months using RNA seq, unbiased proteome analysis of PDBP, BioFIND and HBS CSF samples at 12 months, epigenomic analysis (cell based) of PDBP, BioFIND and HSB samples at 12 months, metabolomics and lipidomics analysis of PDBP, BioFIND and HBS 12 month samples.

Replication costs for longitudinal follow up assays: Analysis of PPMI RNA samples at 12 months using RNA seq, unbiased proteome analysis of PPMI 12 month CSF samples, metabolomics and lipidomic analyses of PPMI 12 month samples.

Additional longitudinal Buy up options:

Total CSF Buy up: Include exRNA seq or exosome analysis of CSF at 12 months from PDBP, HBS, BioFIND

Total Plasma Buy up: Include Somalogic or other unbiased proteomic, metabolomics or lipidomic analysis platform of plasma samples at 12 months from PDBP, HBS and BioFIND.

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From: Wholley, David (FNIH) [T]
Sent: Fri, 24 Mar 2017 13:40:12 -0400
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Cc: Sutherland, Margaret (NIH/NINDS) [E]; Canet-Aviles, Rosa (FNIH) [T]
Subject: AMP PD next steps
Importance: High

Hi Walter and Francis:

(b) (4)
(My last ping was a week ago; radio silence since.)
I am not reading anything in particular into this (I think she is just having trouble corralling everyone who'd need to support this internally), but on our side I think we need to begin moving forward with the partners we have. Some additional work on some of the MJFF samples has already begun (RNA sequencing, some proteomics pilots and the like),

(b) (4)
(b) (4)
Rosa and I just got off a phone call with Todd Sherer and Marg Sutherland where we discussed the first two issues in particular, and Todd agrees strongly with moving AMP PD forward now. This would take the form of FNIH putting together a face to face meeting with our five existing partners (NIH/NINDS, GSK, MJFF, Pfizer, and Verily) to figure out how we apply the \$16M/5 years currently committed to the program in the form of a revised research plan based on the white paper, but with more detailed logistics, budgets, milestones, governance structure, etc. etc. (just as we did with the other three AMPs).

(b) (4)
(b) (4)
Right now we are thinking of having this meeting in mid to late April if we can round up everyone's calendars. While we'd likely want to wait until after the meeting for any formal announcement, if we can just get it scheduled I think we could begin informally to signal to those who may be interested that this is moving forward (say, at the HEVER meeting).

Are you in favor of doing this? Is there anything else you'd like us to do prior to getting this going?

Thanks,
David

From: Wholley, David (FNIH) [T]
Sent: Thu, 16 Mar 2017 20:30:12 -0400
To: Collins, Francis (NIH/OD) [E]; Dolsten, Mikael; Jan Lundberg
Cc: Tabak, Lawrence (NIH/OD) [E]
Subject: FW: 2016_12_16 AMP EEC teleconference draft (003) final clean
Attachments: AMP functional downstream opportunities (b) (4).pdf

Dear Francis, Jan, and Mikael:

Sorry to take up your time yet again,

(b) (5)

(b) (5)

(b) (5) who next meet in late June. The attached was just sent to me by (b) (5); it was drafted by him and (b) (4) as a way of "starting the conversation."

Could you please review this and share your comments, including any recommended next steps, and copy all other addressees on this email? I am copying Larry Tabak as well and of course would welcome any thoughts he may have. If there is some sort of consensus and you think this is worth moving forward we might for example think about next broadening the discussion to include the other EC members and the SC co-chairs (who may have thoughts on how this would apply to their disease/therapeutic area initiatives).

Thank you for your input.

Regards,
David Wholley

From: Wholley, David (FNIH) [T]
Sent: Fri, 7 Apr 2017 10:50:48 -0400
To: Collins, Francis (NIH/OD) [E]
Subject: FW: AMP EC Call Reschedule Update

Hi Francis, sorry to bother you, but we are still having trouble getting everyone together for the next AMP EC. Gretchen and Cheryl have worked on searching multiple dates, but the only one that seems to align with you and at least two of the other participants is May 12 at 7am. (And you will need to take that call from an airport I understand). The one who cannot make it is Jan Lundberg, but to be fair to Jan he could make a couple of other dates that neither Mikael Dolsten nor Paul Stoffels could make. Can you let me know how you'd like to proceed?

Thanks, David

From: Wholley, David (FNIH) [T]
Sent: Fri, 7 Apr 2017 18:45:36 -0400
To: Collins, Francis (NIH/OD) [E]
Subject: FW: AMP EC Call Reschedule Update

Fyi, as you requested

From: Wood, Gretchen (NIH/OD) [E]
Sent: Friday, April 07, 2017 3:02 PM
To: Melencio, Cheryl (FNIH) [T] <cmelencio@fnih.org>
Cc: Wholley, David (FNIH) [T] <dwholley@fnih.org>
Subject: RE: AMP EC Call Reschedule Update

Holding on Francis' calendar. Thanks for getting this together.

Have a great weekend.

g

From: Melencio, Cheryl (FNIH) [T]
Sent: Friday, April 07, 2017 2:56 PM
To: Wood, Gretchen (NIH/OD) [E] (b) (6)
Cc: Wholley, David (FNIH) [T] <dwholley@fnih.org>
Subject: RE: AMP EC Call Reschedule Update

Hi Gretchen,

June 12 seems like the date Drs. Dolsten, Lundberg and Stoffels can attend a call at 7 a.m. eastern time. Dr. Stoffels admin said, there is a J&J Board of directors meeting.....so needs to get off call by 7:50 a.m. Can't give the full hour.

Does this sound like a plan?

Cheryl

From: Wholley, David (FNIH) [T]
Sent: Fri, 24 Mar 2017 15:42:30 -0400
To: Collins, Francis (NIH/OD) [E]
Subject: FW: AMP Executive Committee Telecon

Ugh, again.

From: Melencio, Cheryl (FNIH) [T]
Sent: Friday, March 24, 2017 3:16 PM
To: Wholley, David (FNIH) [T] <dwholley@fnih.org>
Subject: FW: AMP Executive Committee Telecon

I just got this from Pam – for the May 5 AMP Call

-----Original Appointment-----

From: Pamela J Edmonds [mailto:edmonds_pamela_j@lilly.com] **On Behalf Of** Jan Lundberg
Sent: Friday, March 24, 2017 3:14 PM
To: Melencio, Cheryl (FNIH) [T]
Subject: Declined: AMP Executive Committee Telecon
When: Friday, May 05, 2017 7:00 AM-8:00 AM (UTC-05:00) Eastern Time (US & Canada).
Where: (b) (6) France: 0805 770 131 Participant Code: (b) (6) Moderator Code:
(b) (6) Project Code: (b) (6)

Hi Cheryl (b) (6) unavailable to participate. Thanks, Pam

From: Wholley, David (FNIH) [T]
Sent: Tue, 12 Dec 2017 11:11:19 +0000
To: Collins, Francis (NIH/OD) [E]
Subject: Fw: AMP Extended EC 12-15-2017 2nd DRAFT.pptx

Just got this--think we are on the same track.

Sent from my BlackBerry 10 smartphone.

From: Collins, Francis (NIH/OD) [E] (b) (6)
Sent: Tuesday, December 12, 2017 5:18 AM
To: Wholley, David (FNIH) [T]
Cc: Gadbois, Ellen (NIH/OD) [E]; Singh, Jyoti (NIH/OD) [E]; Melencio, Cheryl (FNIH) [T]; Morgan, Emily (FNIH) [T]
Subject: RE: AMP Extended EC 12-15-2017 2nd DRAFT.pptx

Before deleting slides 37 and 38, please consult with Bob Carter – and offer him the chance to make a different cut if these are somehow really important to him.

FC

From: Wholley, David (FNIH) [T]
Sent: Monday, December 11, 2017 9:40 PM
To: Collins, Francis (NIH/OD) [E] (b) (6)
Cc: Gadbois, Ellen (NIH/OD) [E] <gadboisel@od.nih.gov>; Singh, Jyoti (NIH/OD) [E] (b) (6); Melencio, Cheryl (FNIH) [T] <cmelencio@fnih.org>; Morgan, Emily (FNIH) [T] <emorgan@fnih.org>
Subject: Re: AMP Extended EC 12-15-2017 2nd DRAFT.pptx

PS, yes please reach out to Mikael. Cheryl or Emily can you please make the deletions Francis has suggested and resend him the deck to use with Mikael? Thanks

Sent from my BlackBerry 10 smartphone.

From: Collins, Francis (NIH/OD) [E]
Sent: Monday, December 11, 2017 9:33 PM
To: Wholley, David (FNIH) [T]
Cc: Gadbois, Ellen (NIH/OD) [E]; Singh, Jyoti (NIH/OD) [E]; Melencio, Cheryl (FNIH) [T]
Subject: RE: AMP Extended EC 12-15-2017 2nd DRAFT.pptx

Hi David,

Wow, this is better but still seems overly detailed. With 66 slides I fear it will be hard to preserve much time for discussion in our 90 minute call.

Not including the title slides, I count 12 slides for T2D, 21 for RA/SLE, and 15 for AD. That makes me worry most about RA/SLE. I don't see how the team can present 21 data slides in 15 minutes without frustrating the listeners. Can you ask Bob Carter to consider this one more time, and potentially drop a few slides that are not essential? Slides 37 and 38 look like candidates for deletion to me.

Remembering a prior EEC where the introductory remarks from Mikael were elegant and inspiring, but went on WAY too long, shall I reach out to him to divide up that part, and emphasize that the introductory remarks should be very brief? In that regard, I'd recommend dropping slide 7 – it has a lot of details, and Lon and Patrick are no longer involved. Can be referred to verbally.

FC

From: Wholley, David (FNIH) [T]

Sent: Monday, December 11, 2017 4:25 PM

To: Collins, Francis (NIH/OD) [E] (b) (6)

Cc: Gadbois, Ellen (NIH/OD) [E] (b) (6); Singh, Jyoti (NIH/OD) [E]

(b) (6); Melencio, Cheryl (FNIH) [T] <cmelencio@fnih.org>

Subject: AMP Extended EC 12-15-2017 2nd DRAFT.pptx

Hi Francis – As requested, here is the second pass at the slides for the AMP EEC this Friday. We've done our best to work with the co-chairs to prune and improve the slides per your feedback on last week's pre-call. Let us know what you think, including where you think there are any additional opportunities for condensing this. Thanks, David

From: Wholley, David (FNIH) [T]
Sent: Mon, 3 Apr 2017 11:53:43 -0400
To: Collins, Francis (NIH/OD) [E]
Subject: FW: AMP-PD update - likely timing?

Hi, Francis – [REDACTED] (b) (4), (b) (5)

[REDACTED] (b) (4), (b) (5)

The slide for AMP PD currently reads as below. Given the last minute notice we are apparently likely to get I am not sure I would change anything at this point— [REDACTED] (b) (4), (b) (5)

[REDACTED] (b) (4), (b) (5) (And who knows, if so, does Elias want to stand up and say something?)

Please let me know your thoughts and I will have any changes made. Thanks, David

AMP: Parkinson's Disease (PD)

[REDACTED] (b) (5)

Many thanks!
Kim

Kim Pelis, Ph.D.
NIH/OCPL

[REDACTED] (b) (6)

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From: Wholley, David (FNIH) [T]
Sent: Fri, 30 Jun 2017 09:09:30 -0400
To: Koroshetz, Walter (NIH/NINDS) [E]; Collins, Francis (NIH/OD) [E]; Sutherland, Margaret (NIH/NINDS) [E]
Cc: Canet-Aviles, Rosa (FNIH) [T]
Subject: Fw: Any feedback you can give me from yesterday's meeting

This just in,

(b) (4), (b) (5)

(b) (4), (b) (5)

David

Sent from my BlackBerry 10 smartphone.

From: William Marks (b) (6)
Sent: Friday, June 30, 2017 8:46 AM
To: Wholley, David (FNIH) [T]
Cc: David Glazer
Subject: Re: Any feedback you can give me from yesterday's meeting

Hi, David.

To our surprise (in light of initial feedback to pursue discussions with you on the initiative),

(b) (4), (b) (5)

(b) (4), (b) (5)

Bill

On Jun 30, 2017 3:38 AM, "Wholley, David (FNIH) [T]" <dwholley@fnihi.org> wrote:
Know it is early in CA but I am in a meeting with Francis Collins and Walter Koroshetz this morning and they will ask me about where things stand...thanks, David
Sent from my BlackBerry 10 smartphone.

From: Wholley, David (FNIH) [T]
Sent: Tue, 10 Oct 2017 13:54:48 +0000
To: Collins, Francis (NIH/OD) [E]
Cc: Baker, Rebecca (NIH/OD) [E]
Subject: FW: BMS is in

Hi, Francis –

(b) (4)

(b) (4)

(b) (4) Thanks, David

David Wholley
Director, Research Partnerships
Foundation for the National Institutes of Health
(301) 594-6343
fnih.org

Learn more about the FNIH in our 2016 Annual Report: fnih.org/AnnualReport.

From: Collins, Francis (NIH/OD) [E]
Sent: Friday, July 28, 2017 7:41 AM
To: Wholley, David (FNIH) [T] <dwholley@fnih.org>
Cc: Wood, Gretchen (NIH/OD) [E] (b) (6); Wolinetz, Carrie (NIH/OD) [E] (b) (6); Baker, Rebecca (NIH/OD) [E] (b) (6); Adam, Stacey (FNIH) [T] <sadam@fnih.org>; Lowy, Douglas (NIH/NCI) [E] (b) (6); Doroshow, James (NIH/NCI) [E] (b) (6); Tabak, Lawrence (NIH/OD) [E] (b) (6)
Subject: BMS is in

(b) (4)

(b) (4) Done.

He was particularly glad to hear that FDA will be involved, as he thinks there is a great opportunity for precompetitive sharing of biomarker information.

FC

From: Wholley, David (FNIH) [T]
Sent: Fri, 8 Dec 2017 20:39:30 +0000
To: Collins, Francis (NIH/OD) [E]
Cc: Baker, Rebecca (NIH/OD) [E]
Subject: Fw: Can you co-lead the final meeting summary session next week with Francis Collins?

Sorry Francis--you bounced back on my latest email. Thanks, David
Sent from my BlackBerry 10 smartphone.

From: Wholley, David (FNIH) [T] <dwholley@fnihi.org>
Sent: Friday, December 8, 2017 3:34 PM
To: Chris Flores
Cc: Francis Collins; Biarnes, Michael (FNIH) [T]; Menetski, Joseph (FNIH) [T]; Baker, Rebecca (NIH/OD) [E]
Subject: Can you co-lead the final meeting summary session next week with Francis Collins?

Dear Chris,
In going over the final meeting agenda for next week's meeting on the opioids partnership with Francis Collins he asked if you might co-lead with him the final talk summarizing the major findings and action items of the two days on the afternoon of Dec. 13. We (FNIH) would summarize major points on powerpoint as we go along and have that available to you both after the final break to support your joint presentation and any ensuing discussion. Can you please let us know as soon as possible if you'd be willing to do this?
Thanks,
David Wholley
Sent from my BlackBerry 10 smartphone.

From: Wholley, David (FNIH) [T]
Sent: Wed, 3 May 2017 16:06:33 -0400
To: Collins, Francis (NIH/OD) [E]
Subject: FW: Draft note to Celgene - please use THIS version of the complete white paper
Attachments: PACT_Whitepaper_032817.pdf
Importance: High

Francis –

For your note to Mark Alles, please use this version of the complete whitepaper—Stacey tells me the older version I sent you has a formatting error in the appendix—nobody would probably notice, but just to be sure. Apologies for the error. David

Partnership for Accelerating Cancer Therapies (PACT)

FINAL DESIGN WHITEPAPER - FEBRUARY 2017



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National Institutes of Health

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Executive Summary

Recent advances in cancer treatment have offered the prospect of greatly enhanced outcomes, prolonged survival, and cure for some patients. Much of the recent success has been driven by the development of new immuno-oncology (IO) agents, leading to an explosion of translational research as well as investment in the field. To date, however, the improvements in outcomes and cure generated by the monotherapies of these agents are possible only for a minority of patients, and emerging data demonstrate that the greatest impact on cancer treatment will be achieved by combinations of multiple IO agents or of IO and non-IO agents. The successful pursuit of these combination therapies is complicated, however, by the sheer numbers of possible combinations, by high biologic complexity, and by the need for new translational biomarkers and assays to guide which patients should receive which combinations. These challenges are further compounded by the novelty and intensely competitive nature of the IO field, which has encouraged fragmented and at times duplicative research approaches.

To solve these challenges, a systematic cross-sector effort is required to identify and develop robust, standardized biomarkers and related clinical data that support the selection and testing of promising therapeutic combinations. The magnitude of this task and the substantial current knowledge gaps within the field make it unlikely a single stakeholder can execute such a mission alone. As a part of its support of the Cancer Moonshot, the National Institutes of Health (NIH) has proposed a 5-year, ~\$251 million precompetitive public-private research collaboration called the Partnership for Accelerating Cancer Therapies (PACT) to enable achievement of these goals. The initial strategic plan for PACT has been developed through a process led by the Foundation for the NIH (FNIH) with input from 42 key opinion leaders in the cancer field, encompassing representatives from the National Cancer Institute (NCI), U.S. Food and Drug Administration (FDA), academia, and 15 industry partners—AbbVie, Amgen, AstraZeneca, Bayer, Boehringer-Ingelheim, BMS, EMD Serono, Genentech, GSK, Lilly, Merck, Novartis, Pfizer, PhRMA, and Takeda.

PACT aims to accelerate the development of effective combination therapies by enabling critical clinical investigations not covered by others, unifying clinical biomarker investigation, filling knowledge gaps, and integrating information from multiple sources, through two programs:

Program 1: Facilitate robust, systematic, and uniformly conducted clinical testing of basic biomarkers that enable researchers and clinicians to better understand the mechanisms of response and resistance to treatment strategies. PACT will provide a systematic approach to immune and related oncology biomarker investigation in clinical trials by providing standardized biomarker modules, which can be utilized within the PACT programs and across the research community. These modules allow for (a) consistent generation of data, (b) access to uniform and harmonized assays to support data reproducibility, (c) comparability of data across trials, and (d) discovery/validation of new biomarkers for combination immunotherapies and related combinations. Specific elements of the program include the following:

- ▶ Providing a set of basic biomarker modules for uniform clinical application.
- ▶ Establishing a network of 3–5 core laboratories to coordinate, conduct, validate, and standardize biomarker assays.

- ▶ Funding the development of standardized biomarkers for immunoprofiling and exploratory biomarker assays of high relevance.
- ▶ Incorporating biomarkers and data collection standards into trials prioritized through PACT and coordinating their adoption broadly across the IO research community.
- ▶ Creating a comprehensive database that integrates biomarker and clinical data to enable pre-competitive correlative biomarker analyses.

Program 2: Provide scientific coordination for the selection of clinical combination therapy trials important to the field but not already being performed elsewhere, and co-fund such trials with partners. This will be accomplished by the following:

- ▶ Creating and maintaining a “landscape analysis” of combination therapy trials and biomarkers across the entire IO and oncology space, enabling categorization of prospective new trials based on relevance.
- ▶ Selecting and co-funding high relevance combination trials not being performed by other entities, while leveraging significant existing investments (such as in trial networks) made by the government, companies, and nonprofit foundations.
- ▶ Facilitating information sharing by all stakeholders to better coordinate clinical/translational oncology programs, align investigative approaches, avoid duplication of effort, share resources, and enable more relevant high-quality trials to be conducted. This will include active outreach to other IO research efforts on an ongoing basis.

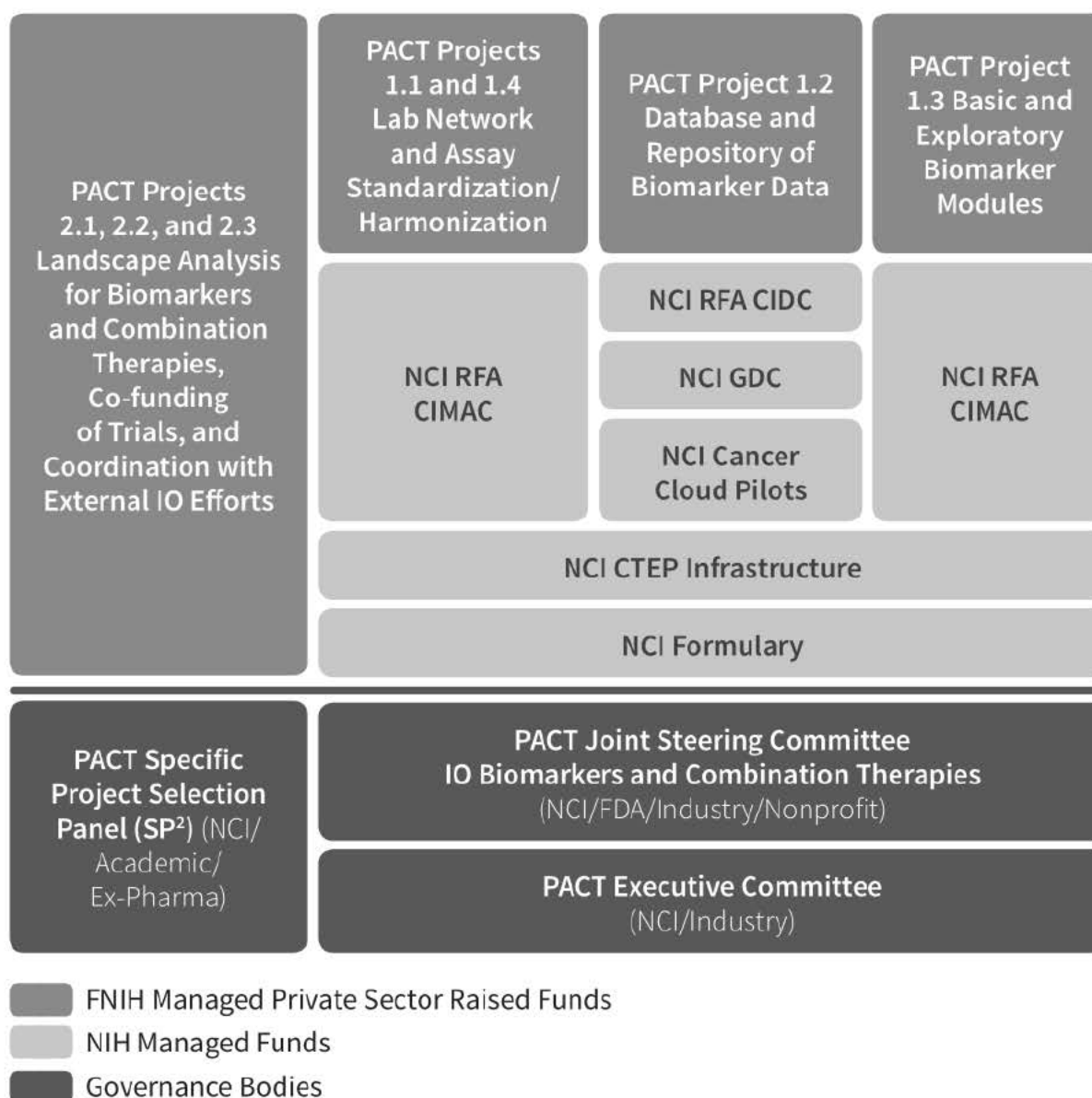
The core laboratory, assay development, and database functions required as part of Program 1 will be built on a solid base of research infrastructure and academic grants funded by NCI. Fortuitously, NCI has recently released several Requests for Applications (RFAs) in November 2016 that are highly germane to the core goals of PACT (see **Appendix 5**). Based largely on existing funding from the Precision Oncology Initiative, with additional planned Cancer Moonshot funding, these RFAs seek applications for ~\$110 million in funding over 5 years beginning in 2017 for a number of Cancer Immune Monitoring and Analysis Centers (CIMACs), a Cancer Immunologic Data Commons (CIDC), and several related initiatives that create integrated multidisciplinary research cores with basic, translational, and computational expertise. Although currently limited as to the number of sites, assays, and data types supported, these grants provide a “shovel ready” foundation for the core lab and database functions required by PACT, particularly when combined with NCI’s recently announced Formulary initiative and its existing national clinical trials network and genomic data management programs.

In addition to supporting these resources, PACT will coordinate and standardize use of existing standardized biomarker assays to most efficiently use available resources. If available, fully validated existing biomarker assays can be conducted through parties outside PACT but channel data into the PACT database, provided assays are performed to PACT standards.

The additional ~\$141 million/5 years required to meet the baseline PACT goals will be raised through FNIH. A majority of these funds will be used to supplement NCI grants, although funds may be disbursed directly through FNIH contracts where appropriate. Additional funds may be sought later for future projects of interest to further PACT partnerships and goals.

A joint governance structure will maintain close involvement by all partners in key decisions, consisting of:

- ▶ An operationally focused PACT Joint Steering Committee (JSC) to direct the research plan and ensure adherence to project milestones
- ▶ A PACT Scientific Project Selection Panel (SP²) to analyze potential therapy/biomarker combinations and advise the JSC regarding fundable PACT studies
- ▶ A PACT Executive Committee (EC) to provide strategic direction, communication with partner leadership, and resolution of policy issues.



Voting participation in the JSC and EC will be split 50/50 between government and private sector partners. The SP² will consist of key academic/NCI oncology experts and scientists with industry oncology experience in drug development who lack significant financial and employment ties to individual companies in order to ensure its advisory role is carried out with objectivity and transparency.

All PACT data will be released publicly as promptly and broadly as possible in keeping with NIH's mission and policy, though also dependent on restrictions in underlying clinical trial and grant agreements. Where feasible, PACT participants will have early access to data; however, data will be retained for analysis and not released publically until study analysis is complete and closed to accrual and treatment in concert with our research agreements for a reasonable time.

The **value proposition** for PACT stakeholders, for the oncology field, and for patients will be considerable, providing immediate:

- ▶ Access to standardized immune biomarker modules, enabling a systematic and uniform analytical approach across trials
- ▶ Access to databases of pre-competitive biomarker analyses, accelerating hypothesis testing and decision-making
- ▶ Access to core facilities with standardized analysis platforms, procedures, and best practices, working with regulatory agencies to ensure the highest quality evidence and documentation, relevant to potential registration and labeling
- ▶ Access to clinical trial landscape analyses for combination therapies and biomarkers across the entire IO space, and the opportunity to align research priorities, avoid duplication of effort, fill gaps, and share resources
- ▶ Opportunities to initiate high relevance trials with company assets for PACT co-funding
- ▶ Opportunity to drive new collaborations resulting from PACT insights and contribute to improving cure rates for patients under the goals of the Cancer Moonshot Initiative

(b) (4)

Introduction

Over the last decade, cancer treatment options have substantially improved, now offering the prospect of greatly enhanced outcomes prolonged survival or cure for some patients. To date, such outcomes are only possible for a minority of patients; however, there is significant potential to expand this benefit to a broad majority of patients in many cancers.

Recently, the positive clinical outcomes associated with progress in cancer treatments have largely been driven by IO agents, which stimulate the immune system to eradicate or control cancer cells. The success of IO therapies in the treatment of melanoma, renal cell carcinoma, NSCLC, as well as some rare tumors such as Merkel cell tumors and Hodgkin's lymphoma has led to a rapid explosion of investments in IO research by the pharmaceutical industry, academic institutions, government, and nonprofit organizations. IO's greatest impact on cancer treatment is expected from combination therapies involving both multiple IO and complementary non-IO agents and will require systematic investigation of a large spectrum of new agents across the portfolio boundaries of individual companies. Despite the great resources invested in IO and related combination regimens to date, the task is complicated by high biologic complexity, the need for translational biomarkers to direct therapy, and the deeply competitive nature of the field, which has led to some redundant research and development efforts, duplication of costs and resources, and the absence of systematic approaches to scientific investigation.

To achieve the desired improvement in outcomes for a majority of patients, a systematic effort across a complex spectrum of pharmaceutical, biotech, academic, government and nonprofit stakeholders is required to effectively test therapeutic combination options and identify biologic markers that direct the right treatment combination to the right patient. This idea has long been gaining followers in the IO field and potential methods for addressing it have been laid out by key scientists in the field (Hoos, Britten, Huber, & O'Donnell-Tormey, 2011). However, the magnitude of this task and the substantial knowledge gaps that still exist make it unlikely that any single stakeholder can execute the task alone. A public-private research partnership such as PACT offers a unique opportunity to address this challenge by coordinating resources across NIH, FDA, biopharmaceutical companies, and patient groups using a focused, collaborative approach. PACT aims to accelerate progress toward improved outcomes by facilitating and enabling critical investigations not covered by others, thus filling knowledge gaps and integrating information from multiple sources across the cancer research sphere.

PACT will establish two program areas that will help determine high priority combination therapies and biomarkers (to be tested by PACT and others in the IO field) and generate the knowledge needed to reduce the number of unnecessary combination trials and improve patient participation in such trials.

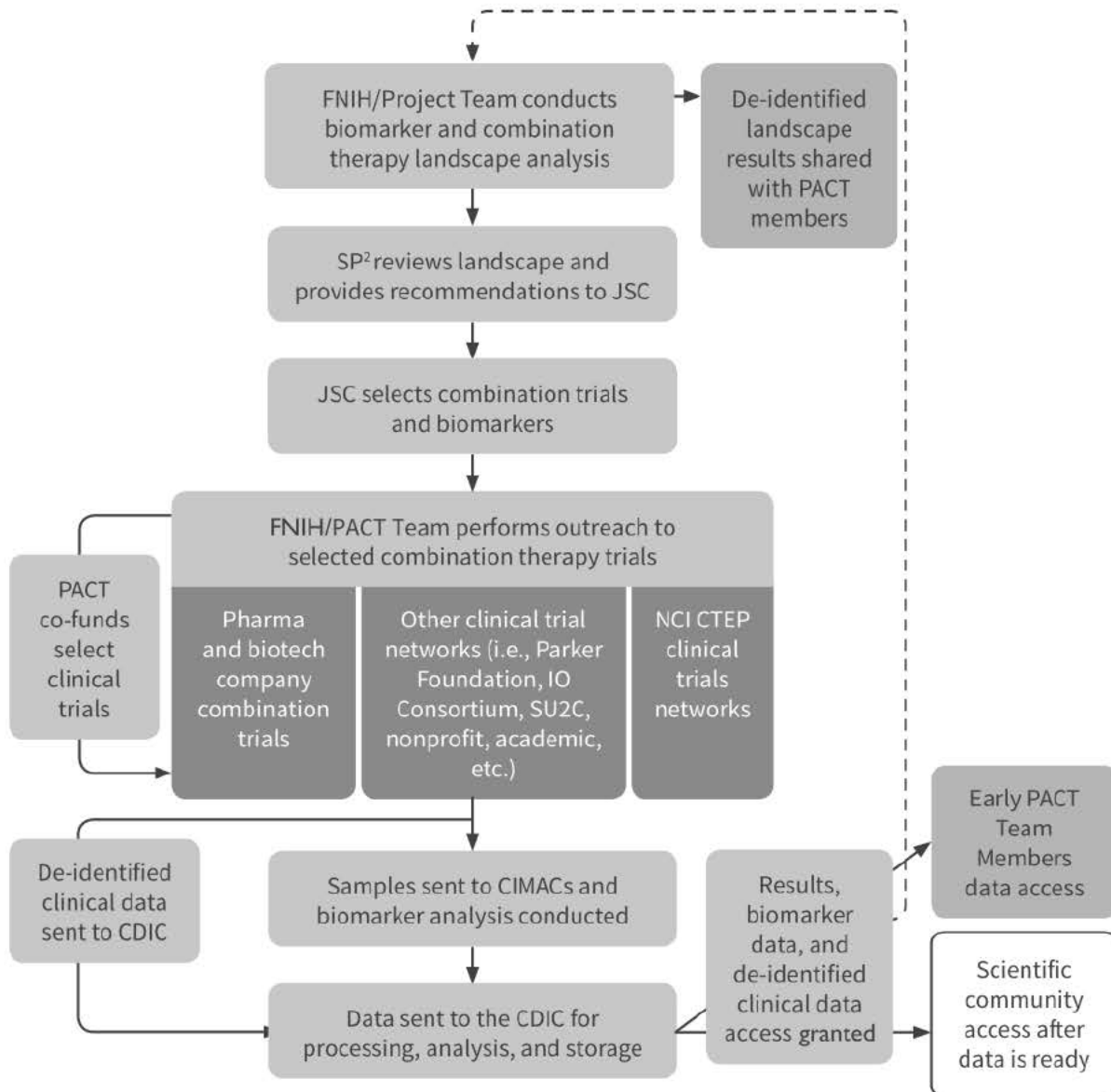
Program Area 1 will facilitate robust, systematic, and uniformly conducted clinical testing of basic biomarkers that enable researchers and clinicians to better understand the mechanisms of response and resistance to treatment strategies. PACT will provide a systematic approach to

immune and related oncology biomarker investigation in clinical trials by providing standardized biomarker modules, which can be utilized within the PACT programs and across the research community. These modules allow for (a) consistent generation of data, (b) access to uniform and harmonized assays to support data reproducibility, (c) comparability of data across trials, and (d) discovery/validation of new biomarkers for combination immunotherapies and related combinations. Specific elements of the program include the following:

- ▶ Providing standardized biomarker modules for uniform clinical application across the community.
- ▶ Establishing a network of 3–5 core laboratories to coordinate, conduct, validate, and standardize biomarker assays and data collection standards.
- ▶ Funding the development of standardized biomarkers for immunoprofiling and exploratory biomarker assays of high relevance.
- ▶ Incorporating biomarkers into trials prioritized through PACT and coordinating their adoption broadly across the IO research community.
- ▶ Creating a comprehensive database that integrates biomarker and clinical data to enable pre-competitive correlative biomarker analyses.

Program Area 2 will provide scientific coordination for the selection of clinical combination therapy trials important to oncology but not already being performed elsewhere, and co-fund a carefully selected subset of such trials with partners. This will be accomplished by the following:

- ▶ Creating and maintaining a “landscape analysis” of combination therapy trials and biomarkers across the entire IO space, enabling categorization of prospective new trials based on relevance.
- ▶ Selecting and co-funding high relevance combination trials not being performed by other entities, while leveraging significant existing investments (such as trial networks) made by the government, companies, and nonprofit foundations.
- ▶ Facilitating information sharing by all stakeholders to better coordinate clinical/translational oncology programs, align investigative approaches, avoid duplication of effort, share resources, and enable more relevant high-quality trials to be conducted. This will include active outreach to other IO research efforts on an ongoing basis.



Value Proposition

The value proposition for participating stakeholders in PACT will be considerable:

- ▶ Access to an infrastructure for incorporating standardized immune biomarker modules in clinical trials, enabling a systematic analysis approach across trials, with reproducible assay results, reduced costs and resources, and enhanced power of correlative analysis
- ▶ Access to core facilities with standardized analysis platforms, procedures, and best practices, working with regulatory agencies to ensure the highest quality evidence and documentation, also relevant to potential registration and labeling
- ▶ Access to a comprehensive database for pre-competitive correlative biomarker analyses, accelerating data acquisition and hypothesis testing, and enhancing decision-making
- ▶ Enhanced reliability and speed of clinically relevant biomarker identification for identifying patients who will benefit from specific immunotherapy agents or combinations
- ▶ Opportunity to be the first to initiate a high relevance trial with the company's asset of interest, co-funded by PACT or its partners (e.g. NCI)
- ▶ Access to and participation in the coordination of clinical and translational programs across organizations in the IO space (pharmaceutical companies, biotech, academia, government, and nonprofits) to align investigative approaches, avoid duplication of effort, share/preserve resources, and thus allow for more relevant trials to be conducted
- ▶ Access to and participation in the creation of an up-to-date clinical trial landscape analysis for combination therapies across the entire IO space, including access to information about relevant investigations not yet covered by any party.
- ▶ Contributing to the goal of the U.S. Cancer Moonshot Initiative of doubling the rate of progress in cancer research and delivering more cures to patients
- ▶ Opportunity to drive new collaborations resulting from the insights of the PACT partnership

Program Area 1: Facilitate robust, systematic, and uniformly conducted clinical testing of basic biomarkers that enable researchers and clinicians to better understand the mechanisms of response and resistance to treatment strategies

Objective

To reach the next level of benefit of immunotherapy for a broader number of patients, it is necessary to understand and characterize the complexity and dynamics of the immune state in cancer patients and the therapeutically induced changes in immune profiles in the tumor and the periphery.

Experimental findings point to the value of biomarkers for cancer immunotherapy in predicting benefit of therapy and understanding the mechanisms of resistance. For example, high tumor expression of PD-L1 is predictive of increased likelihood of clinical benefit from anti-PD-1 monotherapy in patients with NSCLC. Other factors associated with response include high mutational load, inflammatory gene signatures, and tumor-infiltrating lymphocytes. More recently, tumor genomic studies in patients treated with checkpoint inhibitors have revealed mutations in interferon response pathway genes as a potential mechanism of primary or acquired resistance. While these results are promising, systematic testing in larger patient cohorts is needed to confirm preliminary analyses and clinically validate predictive biomarker candidates.

PACT will provide the foundation for harmonizing the use of biomarker assays, data collection, and data banking, as well as optimize systematic biomarker incorporation into clinical trials to understand response and resistance to cancer immunotherapies and to enable new treatment strategies. Specifically, projects under Program Area 1 will address a few key challenges: inconsistent analytical validation standards and assay methodologies across trials, limited power of individual trials, and lack of common data platforms for combined analysis and cross validation across trials. Project 1.1 lays out the biomarkers the PACT team proposes to systematically incorporate into clinical trials as standard practice, while Projects 1.2, 1.3, and 1.4 detail the infrastructure that will be established to evaluate these proposed biomarkers in clinical trials.

Project 1.1—Establishing biomarker modules for systematic and uniform biomarker testing in clinical trials (for PACT and non-PACT studies)

Challenge/Opportunity

The lack of validated biomarkers and the current inability to compare data between clinical trials is a major challenge and partly driven by the absence of uniform and systematic biomarker investigation. This also limits the selection of the most appropriate immunotherapy regimen (single agent or combination therapy) for a given cancer patient based on validated markers. The fundamental lack of understanding of mechanistic interplay between the tumor and human immune system is a major hurdle for patient selection in IO/oncology clinical trials. Lack of data sets that encompass the molecular characterization of the tumor microenvironment (TME) correlated with clinical outcomes needs to be evaluated in appropriately sized patient data sets with a well-defined statistical analysis plan. Moreover, pharmacodynamic biomarkers can provide an early understanding about performance of a new agent or new combination, accelerating decision-making and prioritization. Comparable data sets from most trials conducted by stakeholders in the community, which close data gaps and allow for more systematic analyses, are needed to build validated biomarkers and truly effective patient selection strategies.

Solution

The PACT initiative will select biomarkers that are relevant to the testing of IO agents in clinical trials and that will help researchers to understand key biologic processes and to optimize decision-making in the application of existing and novel therapeutics. Biomarkers will be grouped in “modules”, a set of studies or analyses built around specific biological topics or areas of inquiry (for example, immune cell biology or liquid biopsies). Modules will fall into two categories: basic and exploratory.

Basic modules address commonly used or known biomarkers which can be reliably tested by a broad spectrum of clinical trials. They are fundamental to investigating specific aspects of cancer biology and building baseline data for how immunotherapy treatments effect this biology, have current clinical utility, and should be executable by the majority of trial sponsors in the oncology field. Basic modules must to be usable by a majority of investigators. They are meant to be broadly applicable to most trials and still deliver insights for specific trials.

Exploratory modules will test novel or less well-established markers), and represent an expansion into new areas of science or technology which need further validation or which PACT participants may not be positioned to (or not desire to) study on their own. They are meant to address a specific biology question of interest relevant to each specific trial. Exploratory modules can be added to PACT on an optional basis until enough evidence consistently demonstrates their relevance and applicability so that they can be considered basic standard biomarkers. The exploratory biomarker modules will accommodate new scientific and biomarker discoveries and advances to be introduced and tested by a few investigators initially. Exploratory biomarkers

can cover all types of new assays being developed for tracking treatment response, including imaging, sequencing, proteomics, immunohistochemistry (IHC) multiplexing, and single-cell analysis.

Modules are expected to be used as follows:

1. All PACT-associated studies will be required to test PACT basic biomarker modules—i.e., meaning each study participating in PACT will need to run the basic modules.
2. NCI will adopt PACT biomarker module recommendations for all NCI studies whenever feasible. These efforts will be synergized with the assays being selected for the CIMAC laboratory network.
3. PACT partners and collaborators will be asked to use PACT selected biomarkers with the aim to standardize and harmonize data generation and collection in studies outside of PACT. The use of these biomarkers can either be through the use of the CIMACs or through use of standardized protocols. The process of selecting these non-PACT, external trials to use the CIMACs will be facilitated through the Scientific Project Selection Panel (SP²) and the Joint Steering Committee (JSC).

Each basic biomarker module will employ comparable methods across all participating medical centers and trials. Such comparability will require selection of assays with similar specifications and harmonization of the assays used across participating centers. If achieved, this will allow the cross comparison and coordinated analysis of data across multiple trials.

In addition, the PACT initiative will need to identify clinical trials from which standard biomarkers and/or samples can be collected that can be used to characterize or validate novel Exploratory biomarkers. PACT will place emphasis on identifying combination therapy clinical trials where collecting biomarker information is a high priority to the IO community. The understanding of the mechanisms of response and resistance to IO therapies that will result from the biomarker analyses will aid in the further refinement and selection of combination therapies for future testing.

PACT will not establish its own clinical trials network infrastructure or fully sponsor trials itself, but will partner with and utilize existing clinical trials networks, such as the NCI's National Clinical Trials Network (NCTN) and Experimental Therapeutics Clinical Trials Network (ETCTN), or networks established by nonprofit organizations or industry sponsors. The SP² will identify these trials based on the periodic landscape analyses that will be conducted as part of PACT and pass their recommendations to the JSC. The JSC and the PACT outreach team can work with these external networks or sponsors to help broker a partnership with PACT on those trials resulting in eventual deposition of the relevant biomarker and clinical data into the common PACT database. PACT will also consider providing supplementary funding to conduct these trials in selected cases. This process for trial selection is further described below in **Program Area 2**.

Focus of the Project

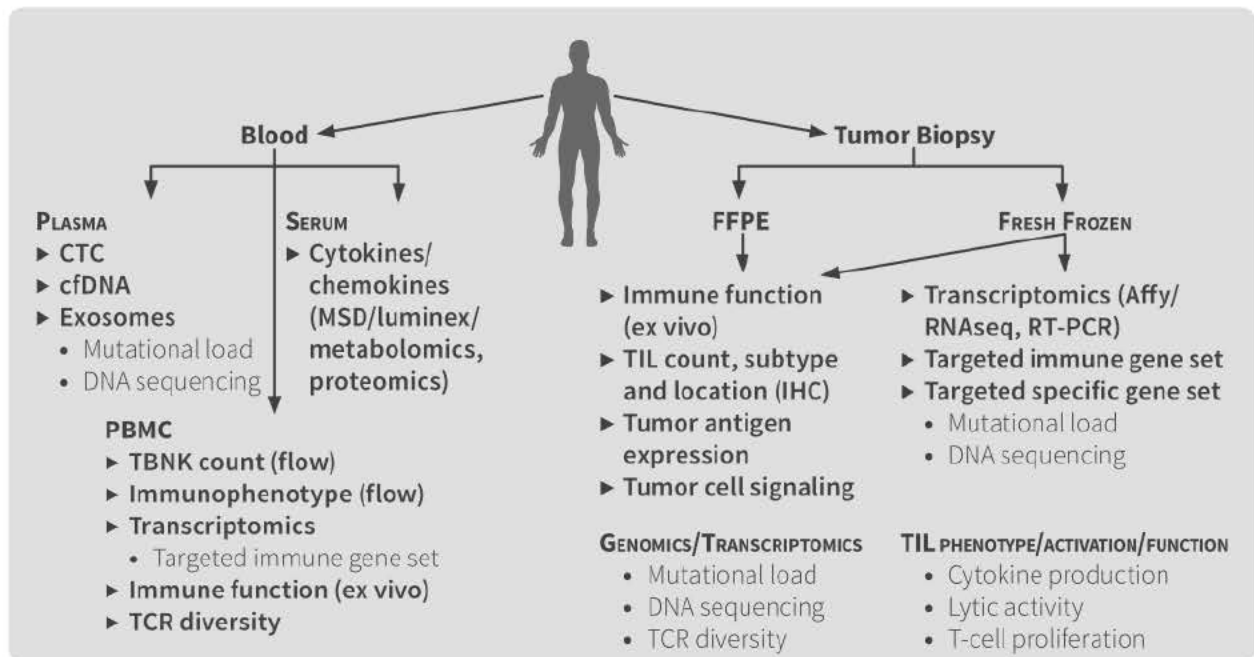
As described above, two types of biomarker “modules” will be pursued for PACT: basic and exploratory modules. Table 1 describes the modules defined thus far by the PACT Working Groups. This table is divided by basic and exploratory modules and defines what tissue collection will be necessary for each.

| TABLE 1. PROPOSED PACT BIOMARKER MODULES | | | |
|--|---|---|--|
| MODULE # | BIOLOGY TO BE STUDIED | DESIRED ASSAYS | SAMPLE REQUIREMENT |
| BASIC | | | |
| 1A | Immune cell biology | Periphery: Flow cytometry and CyTOF—3 (T and B cell panels) Tumor: IHC | Blood, tumor biopsies (core and bulk) |
| 1B | Peripheral cytokines/chemokines | ELISA | Blood/serum |
| 2A | Cancer genetics / somatic mutations | Whole exome sequencing (100X coverage—per standard practice) | Tumor biopsies (core and bulk), blood— isolated DNA 200-500 ng |
| 3A | Transcriptomics of the tumor microenvironment | RNA-seq (150 million reads/sample) | Tumor biopsies (core and bulk), blood |
| 4A | Liquid biopsy | cfDNA assay | Blood— Streck or EDTA tube |
| EXPLORATORY | | | |
| 1c | Immune cell biology | Expanded flow cytometry (innate immune cell panels) | Tumor biopsies (core and bulk), blood |
| 2B | Cancer genetics / somatic mutations | CNVs, SNPs, T and B cell deep receptor sequencing | Tumor biopsies (core and bulk), blood |
| 3B | Transcriptomics of the tumor microenvironment | Single cell/nuclei RNA seq, others TBD | Tumor biopsies—single cell isolates, blood |
| 4B | Liquid biopsy | CTC, cfRNA, exosomes, microvesicles, others | Blood—collection tubes TBD |
| 5 | Defining the microbiome | Microbes and others (see section below) | Stool, saliva, others TBD |
| 6 | Non-immune tumor architecture | IHC, IF, others TBD | Tumor biopsies (core and bulk) |

Basic biomarkers will be standard and mandatory for all PACT biomarker analyses, subject to the sample collection limitations for each trial; exploratory biomarkers will be optional. Biomarkers selected for the basic modules will be harmonized with the assays and platforms named in the CIMAC RFAs. The PACT team has established the priority ranking for mandatory modules: 1a > 2a > 4a > 3a > 1b. Exploratory modules can be conducted at the discretion of PIs; however, if these modules are run, the data generated should be captured in the PACT database. The consistent acquisition of such data across all PACT-related studies will constitute a major advance.

Common Tissue Collection Needs for Biomarker Modules

Any biomarker investigation is only as good as the quality of human samples collected and the reproducibility of the assays used. PACT intends to address both of these issues through careful collection and standardization of biomarker assays. An initial schema for biomarker testing has been outlined as follows:



Baseline Tumor, During Treatment, and Post Treatment (When Possible):

- ▶ Bulk tumor resection (fresh)
- ▶ Core biopsy materials
- ▶ Blood
 - ▷ Standardized whole blood and plasma collection (optional banking protocol)
 - ▷ EDTA tubes, Red top serum tubes, CPT tubes with sodium heparin, and others
- ▶ Bone marrow for hematologic malignancies

- ▶ Standard tissue processing procedures
 - ▷ FFPE
 - ▷ Snap frozen—referred for DNA extraction
 - ▷ RNAlater
 - ▷ Single cell suspension
 - Tissue process with or without enzyme digestion
 - Cell freezing media and standard operation procedure
- ▶ Standard operating procedures (SOP) for dual extraction of DNA and RNA if possible should be explored
 - ▷ Isolated DNA necessary for samples for WES—200–500 ng
- ▶ Emerging tissue processing approaches
 - ▷ Single nuclei recovery for RNA-seq
 - ▷ Smart Tube system for flow cytometry (<http://smarttubeinc.com/index.htm>)
- ▶ Potential biomaterials for microbiome sampling
 - ▷ Serum
 - ▷ Mucosal (Oral swabs, endoscope)
 - ▷ Urine/Fecal
 - ▷ Tumor

Tissue Collection

It is anticipated that tissue collection including blood draws, biopsies and other specimen collections could cost up to \$5,000/patient/time point, if specimen processing is included in the estimated costs. The PACT team anticipates this cost will likely be covered by the groups sponsoring the trials, and that PACT would support the actual conduct of the biomarker assays in the CIMAC laboratories. As a potential optional incentive for trials to participate in PACT, the PACT team could choose to subsidize this cost for trial sites; however, this would need to be a buy-up option, and PACT would likely not be able to support the full \$5,000. This is therefore listed in the budget as a buy-up option at \$7.5 million over 5 years.

Establishing a Biospecimen Repository

Establishing a biospecimen repository will be necessary to allow for easier centralized storage, processing, and accessioning of samples for those trials where further biomarker assays maybe required or desired in the future. This will be especially critical for PBMCs, cfDNA, and other liquid biopsy assays, where a given trial may want to store samples for batch runs or for development of future assays and technologies. Two clear models for biobanking could be established:

- 1) decentralized sample collection, with centralized storage, and centralized database/informatics and
- 2) decentralized sample collection, with decentralized storage, and centralized

informatics. PACT proposes to follow the second model, since PACT trials will be run by multiple organizations, and there will likely be a need to allow the industry trials to retain possession of samples from the trials that they exclusively fund but use PACT biomarker modules or PACT core laboratories. However, PACT will, where possible, recommend that centralized storage also take place.

One option for utilizing existing infrastructure for centralized storage would be to use existing biospecimen repositories at NCI. Both the NCTN and the ETCTN already have biorepositories, and private funding could be used to supplement the grants that already sponsor these repositories. Regardless of where the specimens are stored, the PACT effort will require a centralized accessioning of the samples for initial processing before being sent to the CIMACs for processing. This will allow for accurate tracking of all biospecimens that are part of the PACT effort and could potentially be used for future testing.

Biospecimen Repository Expansion Budget

Supplementing the existing biospecimen repositories at NCI will likely cost ~\$1 million to \$2 million per year to process, accession, and store the samples for the potential 720+ patient samples that are currently due to be collected as part of the CIMACs or external trials. This number would increase if the number of patients were to scale up. This means that a total of as much as \$10 million over 5 years would be necessary for this effort. If PACT were to establish an independently run biorepository, the cost would likely be much greater than this amount. Therefore, \$10 million dollars over 5 years has been added to the PACT budget estimate (see the table at the end of this section.)

1.1.1—Basic Modules

The PACT team had proposed that IHC/flow cytometry (depending on tumor type) and DNA sequencing should be the top priority modules. RNA-seq should be a second priority, unless a particular study mandates a need for this assay. These core modules were selected by the PACT team because they provide a solid knowledge base for cross-comparison of clinical trials that are testing IO therapies. In addition, these modules are well developed and offer good options for standardized assay platforms, as well as analysis techniques. However, a common platform for each module will still need to be selected as part of the research plan for this project for PACT. Platforms and analysis techniques will be selected by the JSC in consultation with the CIMAC team.

Focus of the Project

Mandatory biomarkers will be prioritized by tissue availability and trial needs, but the mandatory modules run for PACT will be standardized across all trials. This means that for some trials not all modules will be used, so PACT has ranked the assays based on amounts of tissue (see above).

Biomarker Module 1: Immune Biology

Focus of the Project

Module 1 is organized into two categories of focus: peripheral samples (i.e., circulating soluble or cell-based biomarkers) and tumor samples. Samples of peripheral blood and resection or biopsy of tumor tissue will be collected, and broad testing is planned.

Module 1a: Immune Cell Biology

Peripheral Specimens

Peripheral samples of blood, serum, or plasma should be collected at multiple time points throughout the course of treatment to allow for longitudinal evaluation of changes in immune biology and, if possible, to correspond with measures of drug exposure. These time points and sample sizes will be dictated by individual clinical protocols. Assays for characterizing the functionality of immune cells by in vitro stimulation can also be developed and will constitute the third flow cytometry panel for Module 1a basic biomarkers.

To analyze peripheral samples, the most common technologies used are flow cytometry and CyTOF for cell based analyses and ELISA-based methodologies for measurement of soluble markers. For a basic evaluation of immune cell biology in the periphery, the panels listed below in Table 2 are recommended. In addition, markers of functional characterization of isolated PBMCs are shown.

TABLE 2. T CELL MARKER PANELS BY FLOW CYTOMETRY

| ACTIVATION | EXHAUSTION | FUNCTIONAL |
|--------------|--------------|--------------|
| LIVE OR DEAD | LIVE OR DEAD | LIVE OR DEAD |
| CD3 | CD3 | CD3 |
| CD4 | CD4 | CD4 |
| CD8 | CD8 | CD8 |
| CD45RO | CD45RO | IFN γ |
| CD69 | LAG3 | TNF α |
| ICOS | TIM3 | GZMB |
| OX40 | CD161 | IL-2 |
| FOXP3 | | |
| CD127 | | |

In Vitro Functional Characterization of PBMCs

- Ag recall
- Epitope spreading
- MLRs

Tumor

Obtaining multiple samples of tumor tissue must be attempted throughout the course of a patient's treatment to allow for longitudinal evaluation of immune response depending upon the needs of the protocol.

Tissues will be collected by resection and/or biopsy. These samples can be fixed, frozen, or used immediately for IHC, gene expression, and TIL analyses (by flow cytometry). Similarly, TILs, once isolated and if sufficient, can be used for in vitro stimulations for cytokine analyses. Specific protocols for sample collection and assay execution are to be defined. For the IHC-based assays, standardized quantitative imaging analysis methodologies will be developed. For flow cytometry-based assays, standardized methods for cell gating will be employed. Tissue is less readily available at multiple sampling points and will be prioritized for use in testing for biomarkers. Evaluation by multiplex IHC will take precedence over flow cytometry and in vitro analyses of immune function, as the recovery of isolated TILs from biopsies may not be sufficient. An example basic panel for IHC is shown in Table 3.

TABLE 3. MARKERS (IHC)

| | | |
|--------|------|-------|
| CD3 | CD16 | PD1 |
| CD8 | CD56 | MHC-1 |
| CD45RO | CD19 | TIM3 |
| CD4 | CD68 | LAG3 |
| FOXP3 | | |

Value Proposition

Data from this module will add to the overall information to understand mechanisms of action for the intervention, mechanisms of therapeutic sensitivity and resistance, and patient selection leading to efficacy.

Approximate Module Budget

Periphery: This estimate is based on a six panel flow analysis, including a measure of receptor occupancy, which should be ~\$2,500–\$3,000/sample. However, this cost may be reduced if we are able to use bulk rates and synergized cost structures within the CIMACs network.

Tumor: This estimate is based on using a simple or single biomarker IHC approach. It should be noted that this approach uses the most tissue.

The cost for this analysis will be ~\$250–\$300/marker. The total cost for the panel is approximately \$3,250–\$3,900/sample. An alternative approach will be to generate multicolor IHC panels that will lead to less utilization of tumor tissue and may provide a moderate cost improvement.

Module 1b: Cytokines/Chemokines Periphery

Multiplex cytokine evaluations using one of the several ELISA-based platforms, such as Mesoscale, ELISA, or Luminex, will be used to test several circulating cytokines in the plasma/serum. The markers will include mediators of immune activation, inflammation, target cell killing, and safety signals such as those of the cytokine release syndrome shown in Table 4.

TABLE 4. SOLUBLE FACTORS

| | | |
|--------------|--------------|----------------|
| G-CSF | IL17 | GZMA |
| GM-SCF | IL2 | GZMB |
| IFN γ | IL4 | PERFORIN |
| IL1 | IL6 | CCL2 |
| IL10 | CXCL2 | CCL3 |
| IL12 | IL7 | CCL8 |
| IL13 | M-CSF | CCL5 |
| IL15 | TGF β | CX3CL1 |
| IL16 | TNF α | CXCL10 (IP-10) |
| IL21 | | CXCL9 (MIG) |

Multiplex Immunoassays**► Immune activation**

- Cytokines
- Chemokines
- Inflammatory mediators

► Safety

- CRS-targeted panel

Approximate Module Budget

This estimate is based on a 29-panel multiplex ELISA-based platform which will be ~\$500–\$600/sample, depending on the choice of platform.

Module 2a: Cancer Genetics/Somatic Mutations

Advances in genome sequencing technologies at affordable cost along with progress in bioinformatics has propelled the field of somatic cancer genetics into a new era. The exponential growth of cancer genome datasets has been justified as a means to identify new cancer genes and pathways that could be the basis for molecular classification of tumors, initiate novel target-based drug discovery programs, and perform molecular profiling of tumors to match therapies with patient-specific genetic alterations. The relevance of mutated antigens in the field of tumor immunology (Gilboa, 1999) has been corroborated by studies of patients receiving checkpoint inhibitors that reported significant clinical benefits correlating with mutational and neoantigen loads (Miao & Van Allen, 2016; Rizvi et al., 2015; Snyder et al., 2014). In addition, tumors with a large number of somatic mutations due to mismatch-repair defects have been shown to be susceptible to immune checkpoint PD-1 blockade therapy (Le et al., 2015). The basis for this correlation is that an increased number of mutations will increase the number of neoantigen specific T-cells capable of eliciting a strong immunogenic response; the very checkpoint blockade that impedes the tumor's ability to suppress neighboring T-cells results in an increase in tumor-cell killing in the presence of a highly immunogenic tumor.

Focus of the Project

To continue to expand on this somatic mutation knowledge and assure that it can be leveraged to determine novel genetic biomarkers related to immunotherapy, the PACT team proposed to conduct whole exome sequencing (WES), taking into account the following principles.

Matched normal tissue: In order to ascertain whether a sequence variant found in a tumor is somatic or germline, it is necessary to sequence normal DNA from the same individual. While tumor-only WES data can be compared to large germline databases to infer whether a mutation is somatic, false positive calls are frequent, particularly in ethnic populations (Garofalo et al., 2016).

Sequence coverage: Mutation load and predicted neoantigens have rapidly emerged as standard biomarkers used in IO trials. The current gold standard laboratory assay for measuring mutation and neoantigen load is whole exome sequencing (WES; $n \approx 20,000$ genes), as opposed to whole genome sequencing (WGS) that provides additional information regarding noncoding somatic mutations that do not produce neoantigens. WES is therefore more cost-effective for immune-oncology purposes. Given that clinical genomics laboratories that are hospital-based or commercial more commonly use gene panels that cover dozens to hundreds of genes, questions have arisen whether these could be adequate for immunotherapy purposes. Dr. Garofalo and colleagues performed comparisons of gene panels with WES. Mutation loads were estimated using large ($n=300-500$) gene panels and were shown to correlate with WES mutational load above a certain cutoff, although by virtue of the limited sampling of human genes contained in gene panels, the vast majority of neoantigens could not be detected. Therefore, it may be concluded that gene panels are substantially inferior to WES in predicting neoantigens (Garofalo et al., 2016). For cost efficiency purposes, PACT will infer trunk versus branch mutations via allelic frequencies from a single tumor site versus multiple tumor sections.

Mutation calling: A recommended approach in the context of multicenter and multiyear clinical studies is to store raw NGS data files in secure databases and reanalyze all data simultaneously using a validated and harmonized pipeline to allow robust analyses of mutation and neoantigen loads with clinical and other data.

Copy number alterations (CNAs): CNAs, which include gains and deletions of DNA segments, can be detected using clinical WES (Rennert et al., 2016). While the relevance of CNAs in predicting the efficacy of immunotherapies is generally less understood, there are reports of specific CNAs correlating with immune phenotypes, and it will be informative to correlate CNAs with other immune markers.

Neopeptide prediction algorithms: Combined use of multiple tools likely gives a better prediction; however, more efforts are needed to accurately assess the immunoprotective properties of neopeptides.

Approximate Module Budget

This estimate is based on analyzing both tumor and normal samples from each patient.

The WES assay cost is \$500–\$1,100/sample (100x coverage, depending on the number of GB). The cost per patient may be estimated at \$2,200 if one assumes 100x WES with 9 GB. The PACT JSC will need to select the optimal coverage to cost ratio that will be acceptable for the WES Basic biomarker module.

Module 3a: Transcriptomic Characterization of Microenvironment

Transcriptional programs in the tumor microenvironment are an important downstream marker of biological processes such as T-cell activation with reported gene expression profile (GEP) signatures including Type I interferon, interferon gamma, T-cell exhaustion, Th1, as well as the cytolytic activity score. Signatures of extrinsic immune suppression such as IDO-1 or TGF-beta expression highlight mechanisms in addition to immune checkpoint blockade that may overcome resistance through combination therapy. In addition to signatures in tumor, pharmacodynamic changes in immune gene expression signatures in blood have been shown to correlate with response to treatment. Approaches to measure mRNA expression span low complexity techniques including qRT-PCR as well as medium complexity technologies such as TaqMan, Nanostring, Luminex, and targeted NGS panels via hybridization capture or PCR amplification, as well as genome-wide RNA sequencing. Several GEP signatures predictive of patient response to treatment have been reported: NanoString signatures in tumor have correlated with clinical outcome in patients treated with PD-1 blockade (Cesano, 2015; Geiss et al., 2008; Man Chow et al., 2016; Piha-Paul et al., 2016; Ribas et al., 2015). Whole transcriptome profiling provides the opportunity for genome-wide characterization of the TME.

Focus of the Project

The PACT team proposes to perform systematic RNA-seq at a depth of 150 million reads across all tumor samples.

In addition to profiling the primary tumor prior to treatment, profiling samples during treatment or upon relapse provides insight into mechanisms of resistance, and point to attractive combination opportunities; it is therefore suggested for those tumor indications where sequential biopsies are possible.

Value Proposition

Transcriptional read-outs of individual malignant and nonmalignant cells from tumor tissue may offer additional insights into cellular states and programs (and heterogeneity therein) that may influence response or resistance to cancer immunotherapies/combinations.

Through supervised or unsupervised learning, GEP modules can be identified and correlated with important clinical outcomes such as prognosis or response to treatment. There are ongoing clinical trials using NanoString GEP signature prospectively to triage patients for different immunotherapies. Novel genes that are co-expressed with established gene expression

signatures can identify new targets and illuminate unknown biology. Fingerprinting approaches can be used to deconvolute immune subpopulations. The expression of candidate neoepitopes can be investigated, as well as effects on alternative splicing.

Approximate Module Budget

The cost of these assays range from ~\$1,000–\$3,000, depending on the platform used for sequencing, the depth of coverage requested, and the type of RNA to be analyzed. Depending on the sequencing facilities and the number of samples to be analyzed, the average cost for a 150 million read standard RNA-seq should be approximately \$1,500/sample. This would make the estimated cost/patient ~\$1,500.

Module 4a: Liquid Biopsy - cfDNA

The difficulty in acquiring routine tissue biopsies in the solid tumor setting hinders the ability of a clinical laboratory to provide real-time information to clinicians and convenient options for patients. Advances across multiple areas—sample preparation, next generation qPCR and sequencing capabilities, rare cell detection and analysis, ultra-sensitive protein detection, storing, accessing, and analyzing very large data sets—are enabling unprecedented multi-dimensional data collection. Liquid biopsy for solid tumors is currently being used, but the complexity of integrating data across cfDNA, exosomes (includes profiling mRNA, miRNA, lncRNA, proteins, etc.), and circulating tumor cells poses a challenge to exploit the full potential of this approach. Moreover, advances in liquid biopsy technologies are occurring much more rapidly than clinical validation of these assays.

Focus of the Project

Biomarkers will be driven by the clinical questions asked. While it is not realistic to propose all possible clinical settings, it is highly likely that immunotherapies will continue to be combined with other targeted agents and therefore biomarker testing will reflect the combined mechanisms of action of all agents. For instance, in nonsmall cell lung cancer, EGFR mutations and ALK fusions will still be tested even as immune-related biomarkers are adopted. For this module, we are proposing a common approach in the pre-analytical phase of testing that will allow for better comparison of analytical testing platforms chosen by individual research teams.

NGS-DNA-seq will be the primary experimental screening platform, which is good for biomarker discovery/research, LDT approaches, and is also the preferred technology in specific settings (e.g., detection of minimal residual disease in certain heme malignancies).

Value Proposition

Testing specimens derived from relevant body fluids (e.g., blood, CSF, pleural fluid, etc.) that may reflect various aspects of tumor pathobiology could better enable clinical decision-making and provide for surrogate endpoints. It could also allow for broader immunoprofiling of patients at more time points before and after IO therapy. This ability to track data from IO treated patients longitudinally and more frequently will allow for more rapid development of novel IO-related biomarkers for treatment development and efficacy. PACT proposes as its basic biomarker module for liquid biopsy to conduct mutation analysis in cfDNA. Specimens for this assay and

other liquid biopsy options can be banked in a biospecimen repository for future processing. Again, this can provide for greater ability to immunoprofile patients using assays developed in the future.

Approximate Module Budget

The cost of this assay will be determined by the cost to collect and process the cfDNA, as well as the costs for the NGS-DNA-seq. The appropriate depth of coverage will need to be selected based on the clinical needs. A safe estimate may be ~\$1,100/sample to align with the WES costs from the DNA module. However, costs could be higher depending on the sequencing coverage required to find the desired mutations in the low amount of DNA present in these samples. The appropriate cost to coverage ratio will need to be determined by the JSC.

Value Proposition for the Basic Modules

Selecting a set of high importance, broadly applicable, and widely testable biomarkers that can be conducted for every PACT-related clinical trial will allow for the systematic cross comparison of IO therapy trial data on a much grander scale than is currently possible. This will allow novel precompetitive predictive biomarkers to be developed for IO therapies of various classes. The ability to cross-compare trials will also allow for complex modeling studies to be conducted to aid in the prediction of better therapy combinations. There are several key questions in the advancement of IO therapies that the biomarkers proposed by this initiative can attempt to answer. These include target engagement, pharmacodynamic activity, mechanisms of sensitivity and/or resistance, as well as identifying the most appropriate patients to treat based on risk/benefit criteria with individual agents or combination therapies. The value of having the data from all of these standardized assays for multiple clinical trials will be to accelerate the discovery of new immunoprofiling markers that can be used to hasten the approval for novel therapies.

Approximate Budget for Basic Modules

The current cost estimations for all the Basic biomarkers, including 3 peripheral flow panels, 1–2 basic IHC assays, WES, and RNA-seq for each patient, range from \$10,000–\$14,000 per time point. (Note: this is greater than the current estimated cost per patient for the CIMACs testing, which is ~\$8,000–\$10,000/sample.)

1.1.2 - Exploratory Module/Assay Development (Buy-up Options)

Evaluation of exploratory biomarkers may also can be performed depending on availability of samples from the periphery and tissue and the specific objectives of the relevant clinical trial. Various stakeholders (e.g., NCI or a company sponsor) can choose to fund these modules based on specific trial objectives or shared objectives across multiple studies. Importantly, exploratory biomarkers or novel assays are necessary for the continued evolution of the biomarker space and can graduate to become part of basic modules once better established. The proposed areas for exploratory marker development are listed below and described in detail in **Appendix 1**.

- ▶ Module 1c: Immune Cell Biology
- ▶ Module 2b: Cancer Genetics/Somatic Mutations

- ▶ Module 3b: Transcriptomic Characterization of Microenvironment
- ▶ Module 4b: Liquid Biopsy—CTC, cfRNA, exosomes
- ▶ Module 5: Defining the role of the microbiome in modulating CI responses
- ▶ Module 6: Non-Immune Cell Characterization of Tumor Microenvironment (differentiation, stroma, vasculature, etc.)

Value Proposition for the Exploratory Modules

Allowing expansion assays to be options for buy-ups for the PACT initiative will allow both the NCI and private sector to fund the development of additional assays that can then be validated to become basic modules that can be incorporated into future clinical trials. This will allow PACT to drive innovation of new IO biomarker development and allow end users to weigh in which biomarkers which markers should be developed. The value of executing these modules through PACT lies in the breadth of use of the markers that can be achieved across the community and the ability to generate consistent data in every trial. The PACT JSC can select and fund desired modules using an RFA or RFP process that insures buy-in and participation of both PACT partners and external trial sponsors.

Approximate Project Budget for the Exploratory Modules

The cost for these expansion modules will of course depend on which assays are selected to be developed and tested. The assay cost will depend the current maturity of the technology, the biomarkers to be developed, and the expense to fully test and validate them. The PACT team estimates an RFA for new biomarker development in clinical trials would cost ~\$1 million to \$2 million per biomarker, which would account for collection of enough data to analytically validate a new biomarker and potentially harmonize it to any existing data if necessary. Assuming development of each assay cost the maximum \$2 million, PACT would hope to fund development of at least one biomarker per year over 5 years for an estimated total of \$10 million for the RFA.

Project 1.2 — Creating a core laboratory network for biomarker analysis

Challenge/Opportunity

Although diagnostic tools have significantly enhanced the depth and comprehensiveness of our abilities to characterize the tumor immune microenvironment, the current use and development of translational biomarkers are limited by insufficient resources for large-scale studies, variabilities in pre-analytic/analytic qualities and standards, and, more importantly, by a lack of common standards and platforms for biomarker data collection (especially for nongenomic “immune” parameters) and inadequate computational tools/platforms for complex, high dimensional analysis.

Consequently, at least three elements are critical to enabling optimized biomarker strategies:

- ▶ Access to biospecimens from early and late stage single agent and combination clinical trials that involve relevant immunotherapy agents
- ▶ Access to laboratory resources and assays with analytical validation and standardization appropriate for achieve clinical biomarker testing
- ▶ Availability of suitable, interoperable data repositories for clinical, genomic, and non-genomic data generated across disparate trials and organizations, similar to that provided by the NCI Genomic Data Commons

Solution

PACT proposes to build on the Research Funding Announcement (RFA) released by the National Cancer Institute (NCI) in November, 2016, to establish a **network of Cancer Immune Monitoring and Analysis Centers (CIMACs) and a Cancer Immunologic Data Commons (CIDC)**, in order to provide consistent, standardized biomarker assays and data repository for NCI's extramural clinical trial networks (links to RFAs in **Appendix 5**). The RFA is open to application from academia, nonprofit and for-profit organizations, and up to 3 CIMACs will be funded with a total budget of \$32.5 million for all 3 centers from NCI over 5 years starting 2017. Each CIMAC will encompass a multidisciplinary group capable of a wide range of analyses for genomic, phenotypic, and functional characterization of the tumor immune system using analytically validated and standardized platforms. The CIMAC-CIDC network will function in a coordinated manner through a central Core Laboratory Coordination (CLC) Committee. The capacity of the proposed CIMACs will provide the mechanism and basic infrastructure needed for objectives of **Program Area 1** of the PACT initiative.

- ▶ The CIMACs to be established through the RFA are budgeted to address the biomarker study needs of early clinical trials of immunotherapy that use the NCI clinical trial networks. PACT has the potential to leverage components of this infrastructure for PACT-prioritized studies. For example, PACT can add new capacity for specific assay platforms or expand the scope of biomarker work for more clinical trials and patients selected by PACT.
- ▶ The clinical trials for PACT-supported biomarker studies can be conducted through a variety of existing clinical trial infrastructures supported by NCI, academia, nonprofits, and industry.
 - ▷ For example, the NCI Cancer Therapy Evaluation Program (CTEP) has an extensive extramural clinical trial network for phase 0 to phase IV trials [including ETCTN, NCTN, the Cancer Immunotherapy Network (CITN) and the Children's Oncology Group (COG)]. CTEP provides standing support for centralized regulatory, data collection, drug distribution infrastructures, and clinical trial conduct in the network sites. CTEP also has a large portfolio of immunotherapy and targeted agents under its collaborative agreements with multiple pharmaceutical companies. Since 2010, CTEP has initiated more than 90 phase I to phase III trials for immunotherapy agents and novel combinations involving immunotherapy.
 - ▷ Other clinical trial mechanisms would also be appropriate for PACT-supported biomarker studies, such as academia, nonprofit funded immunotherapy consortia, and industry-sponsored trial networks.

- ▶ Private sector diagnostic and assay companies and laboratories will be eligible to compete to conduct certain assays for the CIMACs if the CLC determines that this is the most efficient way to conduct these tests.
- ▶ PACT will identify existing/planned trials or develop new trials using existing trial mechanisms and support the implementation of biomarker studies in order to address important scientific questions prioritized by the PACT JSC (as described in Project 2.1 and PACT Governance).
- ▶ PACT will facilitate and maintain close communication with industry, academia, and non-profits for their inputs in identifying opportunities and gaps, prioritizing scientific projects, and sharing expertise and resources where appropriate. This effort is delineated in Project 2.2, described below.

Focus of the Project

To support the goals of the proposed PACT Program Area 1, a network of reference labs will be identified for high priority assay platforms. These “core” biomarkers to be applied are described in Project 1.1. Depending on the stages of development of specific markers and the anticipated purposes of their uses in trials, varying degrees of analytical validation will be required (defined in Project 1.4).

Proposed services for biomarker studies may include quantitative and qualitative methods for immunoprofiling using phenotyping, functional analysis, genomics, epigenomics, transcriptomic, proteomics, metabolomics, or glycomics. Although Clinical Laboratory Improvement Amendment (CLIA)-certified assays are not required for all biomarker studies to be supported by PACT, the selected core laboratories should have the capacity to carry on validation steps from analytical to clinical validation for candidate markers and perform integral biomarker assays (for treatment eligibility) in a CLIA-compliant laboratory that may require an Investigational Device Exemption (IDE) from the FDA. Assay platforms to be employed by reference labs may include, but are not limited to:

- ▶ Multi-spectral flow cytometry, mass cytometry and imaging cytometry
- ▶ DNA-seq for genotyping of variants, T-cell clonality, relevance of T-cell and B-cell epitopes
- ▶ High-throughput transcriptional profiling, RT-PCR, NanoString, RNA-seq
- ▶ Pathological and morphological imaging techniques (e.g., confocal microscopy)
- ▶ Immunohistochemistry (IHC), multiplexed immunofluorescence

The scientific goals of the lab network are to search for patient/treatment selection markers and provide mechanistic insights into immunotherapy agents and combinations. In appropriately selected clinical trials, specific biomarker objectives may include, but are not limited to:

- ▶ Defining the role of inflammation and tumor microenvironment in response/resistance
- ▶ Phenotypic and functional characterization of the immune system, and its impact on response/resistance

- ▶ Functional genomics of tumor and host
- ▶ Identifying tumor target antigens, such as neoantigen, and responding host T-cell receptor repertoire
- ▶ Developing assays to guide rational selection of combinations in individual patients
- ▶ Longitudinal sampling to monitor dynamic changes and target modulation by drug (e.g., in combination therapy)
- ▶ Defining the role/impact of the human microbiome on response/resistance
- ▶ Exploring the mechanisms and predictive markers of immune-related toxicities

A few guiding principles will be followed in the selection of the reference laboratories:

1. The network of laboratories should have the collective capabilities to carry out comprehensive immune profiling assays and analysis on clinical specimens. Based on the current understanding of relevant biomarker platforms, core and exploratory immune biomarker modules are described in Project 1.1, although the lists of the two categories may evolve with time.
2. Depending on the stage of scientific and technical development, some markers will be best tested in individual labs (such as markers utilizing newly developed technologies, and exploratory biomarkers). Others will be developed within a network of qualified labs (such as markers with existing standards and harmonization, and basic biomarkers) or a single high-capacity facility (for certain selected platforms and markers, including both basic and exploratory biomarkers).
3. Each reference lab should participate in, and agree to, the following assay validation and delivery standards:
 - ▶ Adherence to key performance metrics (to be defined) including data quality management systems; development and provision of standardized IO assays using standardized protocols and methods; and banking, tracking, and distribution of biological samples in a compliant manner that would allow dissemination to clinical practice
 - ▶ Delivery of data in standardized formats, for example, in:
 - ▷ IHC: e.g., intensity scores, percent tumor cells at each intensity, H-score, special locations
 - ▷ Next Generation Sequencing (NGS): e.g., BAM files, VCFs
 - ▷ Other scoring methods/algorithms: e.g., immune cell infiltration patterns
 - ▶ Routine, regular performance reviews focused on quality, proficiency testing, and compliance

Value Proposition

The establishment of a network of reference labs will enhance the efficacy, quality, and power of biomarker analysis across immunotherapy trials. By applying standardized sample processing and assay protocols, deviation of test results due to pre-analytical and analytical variations will be minimized, allowing for cross-trial comparisons. Systematic incorporation of key biomarker modules will expand the power of individual trials through combined analysis with other trials.

Approximate Project Budget

The estimate costs for this project is based on the NCI budget for CIMACs, as well as the PACT basic biomarker cost estimates:

(b) (4)

The PACT funds raised to synergize with the CIMACs effort from NCI will:

- ▶ Cover the expenses of the PACT-initiated biomarker projects within PACT selected trials.
- ▶ Expand the testing services of the existing CIMAC network formed from NCI funding to establish assays for biomarker studies in trials prioritized by PACT.
- ▶ Add new assays or platforms to existing capacities.
- ▶ Add new labs with specialized capabilities of novel technologies or expand the general capabilities of the network.

Project 1.3 — Creating a database for all PACT biomarker data

Challenge/Opportunity

A pre-competitive common database or data access platform is particularly important for immunotherapy biomarkers, since individual trials, even large Phase III trials, may not have sufficient power for complex correlative analysis. However, there currently is no widely available repository that contains biomarker data for IO; instead multiple databases are being implemented without coordination and therefore without consistency. Because IO biomarker research is a nascent field, there is a huge opportunity to ensure early data harmonization

and standardization optimization. The definition, collection, storage, and sharing of data and metadata from multiple sources must be standardized: reproducibility of research results and the ability to broadly translate findings will be impossible without such standardization. The data types to be collected, and the adoption or creation of open standards for storing them need to be determined.

Solution

NCI and NIH already have programs to establish unified data repositories that enable data sharing across cancer genomic studies and that are made accessible to the scientific community, such as the Genomics Data Commons (GDC). Construction of both an Imaging Data Commons and a Proteomics Data Commons is also actively proceeding. An NCI Cancer Immunologic Data Commons (CIDC) is in the planning stages and is a natural extension of this concept, and the timing of this effort aligns well with the PACT initiative. Analysis will need to be performed to determine the appropriate model for such a repository, e.g., whether it makes more sense to create a single database to which contributors send their data, or to use a federated model, where researchers can access, combine, and analyze the data as it is acquired from multiple sources. Once a model is defined, collection mechanisms will be created to ensure the data are obtained in a fashion that does not require double or duplicative data entry. This resource will also need to have the capability to house or access corresponding patient level clinical data, i.e. diagnosis, key demographics, treatment history, and outcome history. This feature will be absolutely critical in order to make the resulting biomarker information truly useful.

Another key component for the PACT database will be that contribution of data will be mandatory for all NCI led trials; however, it is understood that for company-driven trials, participating may be limited by the presence of proprietary information. Company sponsors would therefore be allowed to limit the outcome data placed in the repository as necessary. A staged approach will be needed for implementation.

There are multiple NCI programs that have potential relevance to this Project 1.3:

- ▶ **NCI programs where large amounts of relevant data are being collected** already exist and can be leveraged for PACT.
 - ▷ CTEP supported Clinical Trial Networks (as mentioned in Project 1.1). The NCI provides significant resources to the CTEP infrastructure. The NCTN grants a total of approximately \$150 million/year for trials, and the ETCTN grants a total of approximately \$20 million/year for trials. In addition, NCI also issues support contracts (CTSU, CIRB, etc.) for both total that total approximately \$60 million/year. In short, this means that during the first 5 years of PACT, the NCI will invest ~\$1.1 billion/5 years or ~\$230 million/year to conduct clinical trials. Many of these trials are currently studying IO agents or combinations with IO agents. Data generated from some CTEP trials may be used for standardization and harmonization and serve as the initial population of the CDIC.

- ▷ The Quantum Immuno-oncology Lifelong Trial (QUILT) is developing a Master Protocol, and the blanket consent can be adopted to allow the data generated to be broadly shared.
- ▷ The NCI Center of Excellence in Immunology's (CEI) mission is to foster discovery, development, and delivery of novel immunologic approaches for the prevention and treatment of cancer and cancer-associated viral diseases. The CEI collaborates with the CITN, partners with the Society for the Immunotherapy of Cancer (SITC), and fosters collaborations with Biotech and Pharma.
- ▶ **NCI and private sector efforts to develop platforms for immunological data deposition, integration and/or analysis will help guide the CDIC design efforts.**
 - ▷ NCI has an initiative to establish a CIDC (a U24 mechanism RFA is in the planning stages), which would serve as a bioinformatics core center for research data collection, analyses, integration, and data sharing for studies completed by the CIMACs. This effort can be leveraged as the starting point/prototype for the Immunological Data Commons as well as for the data generated by the CIMACs. The short-term goal for this project is to collect and integrate data to allow within- and cross-trial analyses for NCI network studies. The longer-term goal is to provide a common platform to make the data accessible by the IO community and to allow integration with data from outside the NCI. This platform could be used to create common analysis pipelines, as has been done in the GDC for genomic data.
 - ▷ Platforms already exist for various data types or data integration (within industry, nonprofits, data/diagnostic companies, and academia). One example is ImmPORT, The Immunology Database and Analysis Portal, a partnership between researchers at the University of California-San Francisco, Stanford University, the University of Buffalo, the Technion-Israel Institute of Technology, and Northrop Grumman. It is funded by NIAID. ImmPORT can serve as a model for data integration.

Potential synergies between other ongoing efforts and PACT can be used to enhance both programs.

- ▶ Public/private partnerships, which can be leveraged to gain momentum and agreement on issues including the development and use of data standards, data sharing agreements, and the actual sharing of data that is being generated.
 - ▷ Global Immunotherapy Coalition (GIC)
 - ▷ Parker Institute for Cancer Immunotherapy
 - ▷ Bloomberg-Kimmel Institute for Cancer Immunotherapy

- ▶ Complementary projects, where efforts can be made to integrate with varied types of data (genomic, clinical, proteomic, imaging) and to accelerate the discovery and the development of new treatments
 - ▷ NCI Genomic Data Commons & Cancer Genomics Cloud Pilots—focused on genomics data harmonization and accessibility and analysis
 - ▷ NCI Imaging Data Commons (early-stage planning)—focused on imaging data harmonization and accessibility
 - ▷ NCI Proteomics Data Commons (early-stage planning)—focused on proteomics data harmonization and accessibility
- ▶ Other agencies
 - ▷ FDA development of standards for submissions of immunological biomarker data and related documentation designed to support potential regulatory marketing authorization, if applicable
- ▶ Standards development organizations
 - ▷ Clinical Data Interchange Standards Consortium (CDISC), including possible use of Study Data Tabulation Model (SDTM)
 - ▷ NCI Metadata Thesaurus and Cancer Data Standards Repository (caDSR)
 - ▷ Biomedical Research Integrated Domain Group (BRIDG), which is part of ISO
- ▶ Clinical trials conducted by other networks and companies
 - ▷ External trials may not utilize the same assays and platform as PACT studies but would still be useful to include in the database if there was sufficient information about the biomarkers employed to determine analytical validity.
 - ▷ Bridging or compatibility studies would need to be conducted for these trials, and data harmonization would need to be done. These tasks have been accounted for in the budget for this project.

Focus of the Project

Project 1.3 will:

- ▶ Develop a database platform—a “data commons”—that includes both published and unpublished data, to enable data sharing.
 - ▷ Selection of a database technology will need to account for the inchoate nature of this work, providing flexibility and mechanisms to standardize, store, integrate, and interrogate new types of data that will be generated. Clinical, safety, and biomarker data should be contained or accessible through one source. As much as possible, data to be collected should be defined up-front, with the understanding new data types will follow.

- ▶ Identify or enhance data collection tools for the types of biomarker data collected from the basic and expansion biomarker modules defined in Project 1.1, while concurrently developing new tools and data collection standards that may be needed for certain data platforms.
 - ▷ The biomarker data platforms will likely include tumor genomics, T-cell receptor sequencing, RNA-seq and NanoString, IHC or multiplex IF, flow cytometry, cytokine panels, and functional analysis.
 - ▷ As available, additional patient-level data will be included in the database to be paired with the biomarker data, such as diagnosis (e.g. cancer site, histology, staging), patient demographics (e.g. age, gender, race), treatment (e.g. medications, start / stop dates), and outcome history (vital status, disease status, relevant ancillary medications).
- ▶ Provide or develop tools to access and analyze the data and mechanisms to inform clinicians and basic and translational researchers of the challenges of drug combinations and how to optimize treatment for patients.
- ▶ Identify software to support data collection from participating institutions and integration of that data into the data commons.
 - ▷ Role-based security that takes into account HIPAA and FISMA requirements and a variety of authorization models must be an integral part of the system.
- ▶ Identify barriers to data sharing/transparency amongst various drug development parties and develop strategies to overcome those barriers.

Value Proposition

The goal of this project is to create a means to collate, maintain, harmonize, share, and curate the IO data collected in PACT-participating clinical trials, as well as any basic and translational research data that the PACT initiative may identify and request to be contributed to the database, such as that from PACT Program Area 2. The Cancer Moonshot Blue Ribbon panel has specifically called for a “national infrastructure” as a core component of the CITN, and that success will be measured by new, effective treatments “in more patients, across many different cancers.” Achieving this goal requires the ability to integrate and analyze multiple data types from a wide variety of sources. In addition to providing an IO biomarker database for the initial set of clinical trials, the ultimate goal of the repository is to provide access to the research community and enable analyses of the complex systems biology data, which will drive the more systematic and data driven selection of IO combination therapies. This will allow for more efficient drug trials to be conducted by companies and hopefully eliminate duplicative efforts across the field.

Approximate Project Budget

The estimated budget for this Project is based on the NCI Cancer Genomics Cloud Pilot costs and assumes we will be building upon existing resources.

(b) (4)

(b) (4)

1. \$10 million—Acquire storage and compute resources for database platform. Analysis needs to be performed to determine if in-house or cloud-based infrastructure is most appropriate. Security, Authentication, and Authorization components will be developed. Ongoing operations, maintenance, licensing, and leasing costs are included.
2. \$4 million—Develop a database platform, or “data commons,” that includes both published and unpublished data to enable data sharing. PACT will identify the appropriate data model, leveraging existing resources (e.g., NCI Thesaurus) wherever possible and work with community experts to define appropriate data models where standards do not already exist.
3. \$2 million—Identify or enhance data collection tools for the types of biomarker data prioritized to be collected from the basic and exploratory biomarkers defined in Project 1.1, while concurrently developing new tools and data collection standards for certain platforms. This will require establishment of data standards where they do not currently exist and will dovetail with Item 2 above.
4. \$2 million—Develop software/mechanisms to support data submission by participating institutions and integration, validation, and QA of that data in the CIDC.
5. \$2 million—Identify or develop tools to access and analyze the data and mechanisms to enable clinicians and basic and translational researchers to understand the promise and challenges of specific drug combinations and how to optimize treatment for patients. The PACT team understands that this amount will likely not be enough to fully develop all the tools necessary for these endeavors; however, the \$2 million will kick-start the development/enhancement of tools, which could also additionally be funded by grant programs such as Informatics Technology for Cancer Research (ITCR), as well as by private interests. In addition, it is recognized that having a critical mass of data available will be a catalyst for the community to start using it and improving upon existing tools.

This would supplement the \$1 million/year in the CIDC RFA for a total of \$30 million/5 years for both public and private sector funding.

Project 1.4—Assay standardization and validation for high priority basic biomarkers

Challenge/Opportunity

Biomarkers to improve the efficacy of immunotherapy for cancer patients are important tools in clinical management and drug development. Comprehensive profiling of the tumor immune interface with multiparametric technologies that encompass the dimensionality and complexity of the interaction of the tumor and the immune system is needed to monitor and stratify cancer patients for individual therapeutic requirements. A number of candidate biomarkers and platforms with the potential to be developed into assays to predict response to immunotherapy or monitoring have been identified in Project 1.1. The analyses are typically accomplished

through various laboratory assays to measure differences in specific tumor and immune parameters before, during, and after treatment. This may allow the identification of tumor and immune signatures, which correlate with immunotherapy response or resistance or immune related adverse events, and select patients for treatments using the biomarkers, including those identified in Project 1.1.

The diversity of reagents and approaches used in current IO research has produced a large variety of methodologies that are being used to assess the immune systems of humans and data reporting procedures that are frequently not consistent. This situation often hampers data reproducibility among laboratories, which hampers meaningful interpretation of results across studies and could lead to selection of different intent to treat populations. In addition, most of the assays used involve high-throughput multi-parametric “signatures” that require considerable statistical and bioinformatic efforts for proper algorithm development and robust data interpretation. Such capabilities are not currently available to all investigators assaying immune biomarkers and, therefore, biomarker testing is not consistently or uniformly being performed in academic or clinical laboratories due to resource constraints. Furthermore, there is no existing system that can easily integrate analyses across different clinical trials. Given these challenges, which others in the IO field have further detailed (van der Burg et al., 2011), assay standardization will be a critical focus of the PACT effort.

Different approaches to overcome these limitations and to address different technical and logistical challenges have evolved in the process of standardizing biomarkers. The importance of using standard guidelines for both specimen acquisition and analytical methods for biomarker measurements is widely recognized. First, biomarker measurements in clinical trial specimens should use high-quality, fully specified and validated assays. Second, the assay results should be comparable among clinical sites within a trial and between different trials. These goals may be achieved through use of central labs, assay standardization, harmonization, or concordance testing:

- The creation of validated assays with the kind of consistent pre-analytical, analytical, and post-analytical processes required for inclusion into clinical trials can be achieved through the **use of central laboratories** and a centralized biospecimen repository. A central laboratory that is affiliated with the entity sponsoring the trial offers the potential advantages of using the same validated assay to screen all patients and ensuring responsiveness and familiarity with the clinical trial. In addition, flexible, close communication between clinical and research teams during assay validation can be important elements for success in making a biomarker assay viable for use across different studies. Centralized testing provides assurance about the performance of a test, and minimizes differences in test performance or result reporting that can confound the definition of the intent-to-treat population within and across clinical trials. The ability to offer testing at central laboratories allows for integrated testing, sample management, and data-management services, which can facilitate efficient and reliable biomarker testing and data delivery as part of the comprehensive biomarker characterization.

- ▶ An alternative approach that facilitates the comparability and integration of data across multiple laboratories is **assay standardization**. Assay standardization and traceability to reference materials insure the most accurate and meaningful test results. Standardization also makes interpreting laboratory results easier for the physicians providing patient care. Because each assay can have its own reference interval, physicians currently must be able to apply the same reference interval to each test performed by a specific laboratory in order to accurately interpret that laboratory's results and to be able to compare across laboratories. With standardization, analytical results are more likely to be similar across all testing methods so that only one reference interval is needed, significantly decreasing the burden currently placed on physicians in interpreting laboratory results. Standardization is not a one-size-fits-all proposition. It requires development of standard unit measurement definitions, consistent calibration points, and standardized primary and secondary reference methods and/or materials for each analyte.
- ▶ Since reference materials and standards do not exist for many protein and nucleic acid analytes, **harmonization of biomarker assays** is another approach. Harmonization allows for the establishment of assay-specific protocols in individual laboratories while minimizing differences in assay performance due to assay-related variables. The use of identical reagents, instrument platforms and/or protocols and scoring criteria across laboratories is one solution, but this may not be feasible across many different laboratories. The harmonization process involves the participation of multiple laboratories in a consortium-based iterative testing process to identify the variables crucial for assay performance. To begin, individual laboratories participate to perform parallel quality control experiments on replicate samples with assay proficiency panels using the labs' own reagents, instrumentation, and protocols. A central laboratory manages logistics for the proficiency panel, receives raw and analyzed data sets from each participating laboratory, and provides independent central data analysis. During initial proficiency panels, variables are identified that impact test performance across the labs. Subsequent independent panels are then used to optimize protocols and harmonize the assay-related variables across laboratories (van der Burg et al., 2011).
- ▶ An example of an effort that addressed **concordance testing** or a comparability approach across multiple IHC-based PD-L1 tests was the Blueprint PD-L1 IHC Assay Comparison Project, which is a collaboration between the International Association for the Study of Lung Cancer, American Association of Cancer Researchers (AACR), four pharmaceutical companies (Bristol-Myers Squibb, Merck & Co. Inc., AstraZeneca PLC, and Genentech/Roche), and two diagnostic companies (Dako/Agilent and Ventana/Roche). Further detail and other examples of harmonization projects are in **Appendix 2**.

Solution

A part of methodological improvements for tumor and immunoprofiling assays provided in PACT will involve the creation of validation guidelines for immunoassays to support immune biomarker application and development for clinical trials. Part this project will enable the standardization and validation of assays to interrogate the IO biomarkers identified in Project 1.3. Standardization

and validation of the assays to be used for multisite trials and across different trials should minimize variability in assay results and provide an opportunity for comparability across sites and studies. Achieving a high level of data reproducibility and data comparability will help to accelerate the development of therapeutics targeted to specific biomarker-selected patient populations.

Focus of the Project

This project will likely have two aspects: 1) assay standardization/harmonization and 2) establishment and distribution of standard operating procedures (SOPs) and best practices.

1. Assay standardization/harmonization

First, 1–2 core laboratories from within the core laboratory network will be selected to validate existing assays for the PACT basic biomarkers. These laboratories should be able to establish technically and analytically validated assays that include several continuous steps of biomarker development. Technical and analytical validation refers strictly to the performance of the assay. Assay clinical validation occurs as part of the outcome analysis in clinical trials that ensures that the assay performs robustly according to predefined specifications (fit-for-purpose) that will establish acceptable criteria for use in future studies. Clinical utility, which refers to establishing the use of a biomarker test leads to a favorable benefit-to-risk balance, that is, guides clinical decisions that lead to better outcome, should also be planned.

PACT projects can be tasked to address various aspects of assay validation and standardization for selected markers based on the PACT JSC recommendation:

- **Evaluation of pre-analytic factors:** An important step in biomarker validation is the evaluation of **pre-analytical factors** that may affect assay performance due to specimen-related variability. For immunotherapies, for example, there may be a need to monitor *ex vivo* immune responses in phenotypical or functional assays, which require high-quality samples to ensure reliable analytic output. To ensure that optimal pre-analytic processing regimens are followed, SOPs for controlling specific biomarker development steps are essential. In general, best practice metrics can be defined for various parameters depending on the specimen type to be used. For instance, protocols for blood collection and processing, tumor collection, sample fixation and processing, and storage media optimization are often developed. To improve standardization of specimens, NCI has published best practice guidelines for biospecimen collections (National Cancer Institute, 2011). PACT will endeavor to follow these published guidelines where possible and make modifications where needed. Additionally, pre-analytical considerations for certain assay types can be found in **Appendix 2**.
- **Technical and analytical validation:** Analytical validation involves establishing the performance of an assay for its intended biomarker measurement. Analytical validation studies can include 1) accuracy, 2) precision, 3) analytical sensitivity, (4) analytical specificity, 5) reportable range of test results for the test system, 6) reference intervals (normal values) with controls and calibrators, 7) intersite reproducibility if the assay is to be performed in multiple laboratories, and 8) establishment of appropriate quality control measures (Becker,

2015; Jennings, Van Deerlin, Gulley, & College of American Pathologists Molecular Pathology Resource Committee, 2009; Landis & Koch, 1977; Linnet & Boyd, 2012; Mandrekar & Sargent, 2009). There are also validation study considerations depending on the type of assay and specimens that are used. For example, reader precision studies are needed for IHC tests, whereas molecular assays require accuracy studies. Whether the assays are for integral, integrated, or exploratory biomarkers, they must be fit-for-purpose and meet the acceptable criteria defined for the intended use in patients and trials. PACT will be able to use samples from trials that participate to perform technical validation of assays, when deemed necessary and approved by the trial sponsored.

- **Clinical validation:** After an assay has been analytically validated, PACT-associated laboratories may also be able to carry out **clinical validation** of the assays to determine whether the assay result has a clinically meaningful correlation with the condition of interest—for example, whether the assay reliably divides the patient population(s) of interest into distinct groups with divergent expected outcomes to a specific treatment. The laboratories will be asked to perform assays for integral biomarkers (for treatment eligibility) in a CLIA-compliant laboratory, and use of the test in a trial may need to be performed under an IDE from the FDA if it is a significant risk trial. This aspect will not be a requirement of all PACT-associated laboratories.
- **Assay harmonization and concordance testing:** For certain biomarkers and assay platforms, there may be a need for assay harmonization between labs or testing of concordance between validated assays. Such projects will be prioritized by the PACT Joint Steering Committee depending on the scientific importance or the clinical trial needs of PACT to have these assays become part of the basic biomarker modules and uniformly performed across all PACT-associated trials.

2. Establishment and distribution of SOPs and best practices.

The PACT core laboratory network group will create a **committee** to coordinate efforts and to promote synergistic research efforts among the core laboratories. This Core Laboratory Committee (CLC) will meet monthly and review to progress in developing biomarker assays and report its findings to the PACT JSC. It would operate as a work group of the JSC, but would remain a separate entity reporting to controlled by the NCI CIMACs. The CLC will select best practices from the CIMACs and generate and distribute SOPs and other materials among the core laboratories to keep the assays standardized and updated with best practices. These SOPs and materials will be shared with external partners that wish to run the PACT modules in their trials and contribute their data, but not use the PACT core laboratory network.

Evaluation and prioritization of biomarkers and platforms for which validation will be required will be assessed by the PACT JSC.

Value Proposition

The biological complexity of the tumor and immune system interaction poses multiple challenges associated with technical development of clinically applicable assays when evaluating different variables as markers of clinical benefit to immunotherapy. However, each of the potential biomarkers and their associated assays requires high-quality validation in order to be used effectively in clinical applications. Considering the increased relevance and emphasis on biomarker development in cancer immunotherapy, there is an enormous need to facilitate and improve the steps to demonstrate clinical value of molecular diagnostics in this space. PACT will apply standardized approaches for biomarker validation described above, when necessary, to enable more efficient assay development to identify IO-relevant biomarkers, which are crucial to guide personalized therapy and for advancing IO options for cancer patients.

Approximate Project Budget

The cost of this project will be tied to the time and resources necessary to establish an analytical performance of each assay. Because flow cytometry, IHC, DNA/RNA sequencing, and other analytical methods constitute a large segment of the molecular characterization of the tumor and immune profiling, they will likely be the first validated for specific use. The estimated cost for running each assay for validation is \$500–\$1,000/sample, depending on the assay type (~\$500/sample for IHC versus ~\$1,000 for some flow cytometry panels), with the likely need to perform comprehensive analysis of 100 samples to validate any assay head-to-head. Cost for one assay comparison would then be ~\$50,000–\$100,000. For more complex assays, there could be additional costs even beyond this estimation. There would also be additional costs associated with time of the technical staff, biostatistical staff, and computer scientists for stand-up of the assays within the labs and the postanalytical phase of assay validation. The hope is that these costs could be partially defrayed since the CIMACs will already be established. In addition, PACT would hope that the cost for the samples for these validation assays would also be low due to the availability of banked samples in the PACT biorepository.

Project management and organizational support for the panel and team will also be required in order to assemble and keep current the materials for the drafting and review of the SOPs. A small team to do this—contracted separately from the core laboratory network and including one project manager and one science writer at full-time salary and benefits, plus the meetings and supplies—would cost ~\$400,000/year.

The following table summarizes the total budget for Program Area 1:

Program Area 1 Consolidated Budget

| PROJECT PLAN SECTION | BUDGET ITEM/ PROJECT GOAL | (b) (4) | TOTAL PROJECT COST |
|--|--|---------|--------------------------|
| Project 1.1.1 and 1.2 | Create core laboratory network to conduct biomarker assays | (b) (4) | (b) (4) |
| Project 1.1.2 | Develop new IO biomarkers | | (b) (4) |
| Project 1.1 and 1.4 | Expand biorepository capabilities for sample storage | | (b) (4) |
| Project 1.3 | Create database to bank IO biomarker data from clinical trial | | (b) (4) |
| Project 1.4 | Standardize and harmonize biomarker assays for IO therapy | | (b) (4) |
| PROGRAM AREA 1 | | | \$205.75M |
| Program Area 1 — “Buy-up” Option ► Supplement to defray costs of additional tissue collection at clinical sites | | | |

Program Area 2: Provide scientific coordination for the selection of clinical combination therapy trials important to the field but not already being performed elsewhere, and co-fund such trials with partners

Project 2.1 – Landscape analysis and literature review of biomarkers being developed and IO and other therapy combinations being tested across the oncology field

Challenge/Opportunity

One of the primary hurdles the PACT initiative will face is that the field of IO is moving at such a rapid pace compared even with other portions of the cancer research and clinical fields. This accelerated pace of research, drug development, drug release, and clinical use of IO therapies will make it challenging for PACT to select which biomarkers to develop and test unless these deliberations are accompanied by a “real time” effort to gather information on all of the current trials and related activities in the field. Specifically, the Scientific Project Selection Panel (SP²) and Joint Steering Committee (JSC) will need guidance on which biomarkers and combination therapies are being tested or are in development. A crucial piece to development of this guidance will be to produce it quickly as the timeline will need to parallel the IO drug development pace.

Solution

To stay current and synergize most effectively with other efforts in the IO and oncology field, we propose to have a small team of science researchers and writers regularly conduct a landscape analysis of critical efforts in the IO field. The first fully comprehensive landscape analysis will occur just after the launch of the PACT initiative. This comprehensive analysis will likely take approximately 1–3 months to fully research all publically available information about ongoing biomarker and combination trials within the IO space that have taken place to date, and then compile that data into a digestible format for the SP² for review. This group will also engage with PACT company members to acquire data on the emerging company trials, as well as to gain any organizational insight into the IO landscape that can assist in the selection of combination therapies and biomarkers to be addressed through PACT.

The landscape analyses will include publically available data from publications, websites (e.g., clinicaltrials.gov and others), abstracts, and corporate websites and publications, as well as insights gleaned directly from conversations with relevant industry representatives, both PACT and non-PACT members as appropriate. Both public and private information will be collected, and the FNIH (or its contractor) will act as a neutral third party to collect the data. Two versions of a summarized report will be generated: 1) a high-level summary devoid of any proprietary data, which can be reviewed by the entire PACT JSC to assist in decisions, and 2) a more detailed summary which may include some proprietary data—as necessary and if willing to be shared—to be reviewed only by the SP² (which, it should be recalled, will include no members of competing pharmaceutical companies, but only academics and ex-company members with no conflicts of interest). The authors of the landscape analysis as well as the SP² members will be bound by confidentiality agreements.

From this analysis, the team will create and maintain an up-to-date summary clinical trial compendium for combination therapies and biomarkers in development from current and emerging data across the entire IO space enabling categorization of trials into three types: 1) highly relevant to the entire IO field, funded trials; 2) proposed trials that are highly relevant to the IO field but currently unfunded; and 3) trials of low relevance. The SP² will review this compendium and use it to make recommendations to the JSC about which trials and resulting biomarker modules PACT should pursue, and which trials PACT should help to co-fund. As a secondary feature, the SP² will also be able to make recommendations to the IO outreach team about which groups to work with to develop cross-fertilization efforts and which other groups to approach about depositing their trial data into the PACT database for harmonization with PACT biomarker modules.

After this initial landscape analysis is generated, it will be shared with the appropriate governing bodies for PACT to allow them to make their initial decisions. A landscape update will be conducted biannually each year the PACT initiative continues. These biannual updates will take place in the month immediately following the annual meeting for the American Society of Clinical Oncology (ASCO) and the European Society for Molecular Oncology, which usually occur in early summer and late fall. These meetings usually have the largest release of data from all stakeholder groups relevant to the PACT initiative and therefore will be ideal targets for the landscape updates. While these meetings will be the primary target for data review due to the large amounts of new data released, the analysis will also be sure to account for data released at other meetings in the time between landscape scans, such as the ASCO, American Society of Hematology, American Association of Cancer Research annual meeting, and others. After each update, a report similar to that generated after the initial landscape analysis will be prepared and shared with appropriate committees.

Value Proposition

A full picture of current and upcoming biomarker testing will allow the PACT teams to continuously update its pipeline of basic and exploratory biomarker modules. Having the most current list of IO combinations being tested will also allow the PACT initiative to approach

the right individuals with whom to discuss incorporating their markers and trials into PACT, and help construct a knowledge base to help guide the field with respect to choosing future combination studies.

The landscape analysis will also help support the active outreach to other groups that are working in the IO space described as part of Project 2.2.

Approximate Project Budget

(b) (4)

The total cost for this project is therefore estimated at ~\$1 million dollars over the 5 years.

Project 2.2 – Selection of trials with high-priority combination therapies and biomarkers for co-funding by PACT

Challenge/Opportunity

As mentioned above, PACT will not establish its own clinical trials network infrastructure or fully sponsor and conduct the trials itself (i.e., contract with selected clinical sites; finance and monitor patient accruals; hold INDs; conduct safety reporting; submit registrations etc.), but will work with existing trial networks to implement clinical trials that will use the PACT biomarker modules. These clinical trials may come from the NCI's clinical trial networks (e.g., ETCTN, NCTN, CITN, and COG), industry, academic investigator-initiated trials, or nonprofit consortia (e.g., Stand Up 2 Cancer, Parker Foundation IO Consortium), provided groups are willing to work with PACT and implement the biomarker modules within them. Partner trials will be selected by the PACT JSC based on the landscape analysis described in Project 2.1 after review by and based on the recommendations of the SP². JSC will next work with an outreach project team from FNIH to help broker a partnership for PACT biomarkers on those trials and eventual deposition of the data into the common database. This outreach project team could also encourage companies or other trial networks to initiate new trials using some of the high-priority combinations identified by the SP² if these trials are not currently in the pipeline. (This is further described in the description of Project 2.3 below.) The PACT team also recognizes there will be a few particularly high-value combination trials to be conducted that need some supplemental funding in order to be launched, as they may not be within the short-term pipeline of any company. PACT will work

to facilitate partnerships between the necessary companies to initiate these trials, PACT can consider providing supplementary funding to conduct these trials through mechanisms already available, or it may choose to institute a unique RFA mechanism for these trials.

The following are some examples of how this will work:

- ▶ **Example 1: PACT initiates new trials for novel combinations and supports the relevant biomarker studies:** A new high-priority treatment or combination regimen is identified by the SP², and the JSC decides it should be a PACT trial because the biomarker and clinical objectives would fill critical gaps in the field. However, the companies with the compounds of interest are not able to prioritize their resources to fund the clinical and biomarker studies in their entirety. (Or, alternatively, PACT proposes new trials for combinations already in clinical testing, but finds that additional studies with alternate designs or clinical settings are needed (e.g. with pharmacodynamic endpoints or biomarker stratifications) to address critical biomarker or clinical questions not otherwise tested.) In this case, PACT approaches the companies and offers to help support the costs of the biomarker testing. The size of the trials may range from small phase I/pilot studies to larger phase II trials. As an example, one could estimate a trial of 50 patients to cost ~\$6 million. PACT could invest ~\$2 million to conduct the biomarker assays and some site supplements. If the trial were to be conducted through the CTEP infrastructure, CTEP would supplement payments to trial sites to cover ~\$2 million. This would then leave the companies with only ~\$2 million to raise to conduct the trial. It is the hope that this reduced cost would incentivize the companies to participate in the trial as part of PACT.
- ▶ **Example 2: PACT supports biomarker studies in ongoing/planned trials:** The SP² identifies an existing clinical trial involving immunotherapies that are suitable for high-priority biomarker studies, and the JSC decides it would fit well as a PACT trial. However, the companies sponsoring the trial are only able to conduct limited biomarker assays. In this case, the PACT team will approach the sponsoring companies (or clinical trial network, depending on the trial structure) and ask them to collect samples to run at least the basic biomarker modules in their trial. In this case, PACT pays for the testing of these biomarkers only. If one assumes this is a phase I/II trial with a cohort of 50 patients, then the PACT supplement for this trial would consist of \$500,000 to conduct the biomarkers plus an additional \$500,000 to supplement collection and storage of the additional samples needed for the biomarker testing. This would result in a total of an approximately \$1 million trial supplement. Trials of this type could come from either the NCI Clinical Trials Networks or from the private sector.
- ▶ **Example 3: PACT supports biomarker studies in completed trials:** The SP² identifies a clinical trial of a high-priority therapy combination or biomarker objectives that has already been conducted and for which properly banked biospecimens are available, and the JSC decides it would fit well as a PACT trial. PACT funds the conduct of basic biomarker modules on the samples. (This may be phase I, II, or III trials.) The cost to run the basic biomarker modules would be tied to the number of patient samples. If the trial collected 200 patient samples, the cost would be ~\$2 million to run the basic biomarker assays.

As noted in each of the examples, once drug combinations of interest or existing clinical trials are identified and the decision to provide PACT support has been made, the PACT outreach team from Project 2.3 will work to recruit the necessary partners. In addition, as the PACT program develops, a mechanism can be established for teams to send proposals for priority combination therapy trials to the JSC for review independent of the landscape analysis.

Value Proposition

Co-funding trials through PACT will enable trials that would not normally be conducted by companies on their own, but that have high potential value to the field, to be conducted, with the resulting data shared with the research community. Co-funding could also be a means to conduct retrospective biomarker assays on banked samples from high-priority data that would substantially add to our understanding of the science behind IO and related combinations.

Approximate Project Budget

Costs for this project will be partially accounted for in the biomarker budget for Project 1.1, as one of the main aspects of co-funding will be to pay for testing of the biomarkers for the trials. However, it is anticipated that there will also be a need for funding for an RFA to support 5–10 of the highest-priority trials to be conducted during the first 5 years of PACT. It may also be possible to create an RFA for clinical trials through either the ETCTN or NCTN. (b) (4)

(b) (4) Co-funding could range from simple biomarker support to partial trial funding. The RFA could be administered either through FNIH or NCI depending on the desired needs and structure of the partnership.

Further PACT Trial Co-Funding (Optional)

The amount for co-funding detailed here represents an initial investment by PACT to assist in getting important trials conducted. (b) (4)

(b) (4) This further funding can be determined in future years and on a trial-by-trial basis with the funding partners if the PACT model proves to be successful.

Project 2.3 – Active outreach and coordination with other ongoing IO/oncology efforts

Challenge/Opportunity

As a logical counterpart of its biomarker development, assay standardization, data integration, and trial (co-)funding mission, PACT is designed to serve as a clearinghouse and coordination point for information and insights on potential IO and combination therapy research. Given this PACT will need to coordinate actively with the many existing and emerging public and private research efforts in the field.

Solution

A scientific program management team at FNIH and experienced in facilitating the work of public- private partnerships will leverage the information from the landscape analyses that are ongoing in Project 2.1 to conduct targeted outreach and establish external collaborations with similar programs supported by biopharmaceutical companies, nonprofits, academic medical institutions and government agencies. This team will work to coordinate efforts continuously across all active IO efforts, avoid duplication, share information, and ultimately meet the PACT objective of a systematic translation, evaluation and validation of biomarkers and assays.

Value Proposition

A proactive, constant outreach to and involvement of other IO/combination efforts will allow the most efficient use of the investments of PACT stakeholders and there sources available in the field, given biological complexity of immunotherapies and related combinations and the breadth and depth of what must be learned in order to deliver effective treatments to patients.

Approximate Project Budget

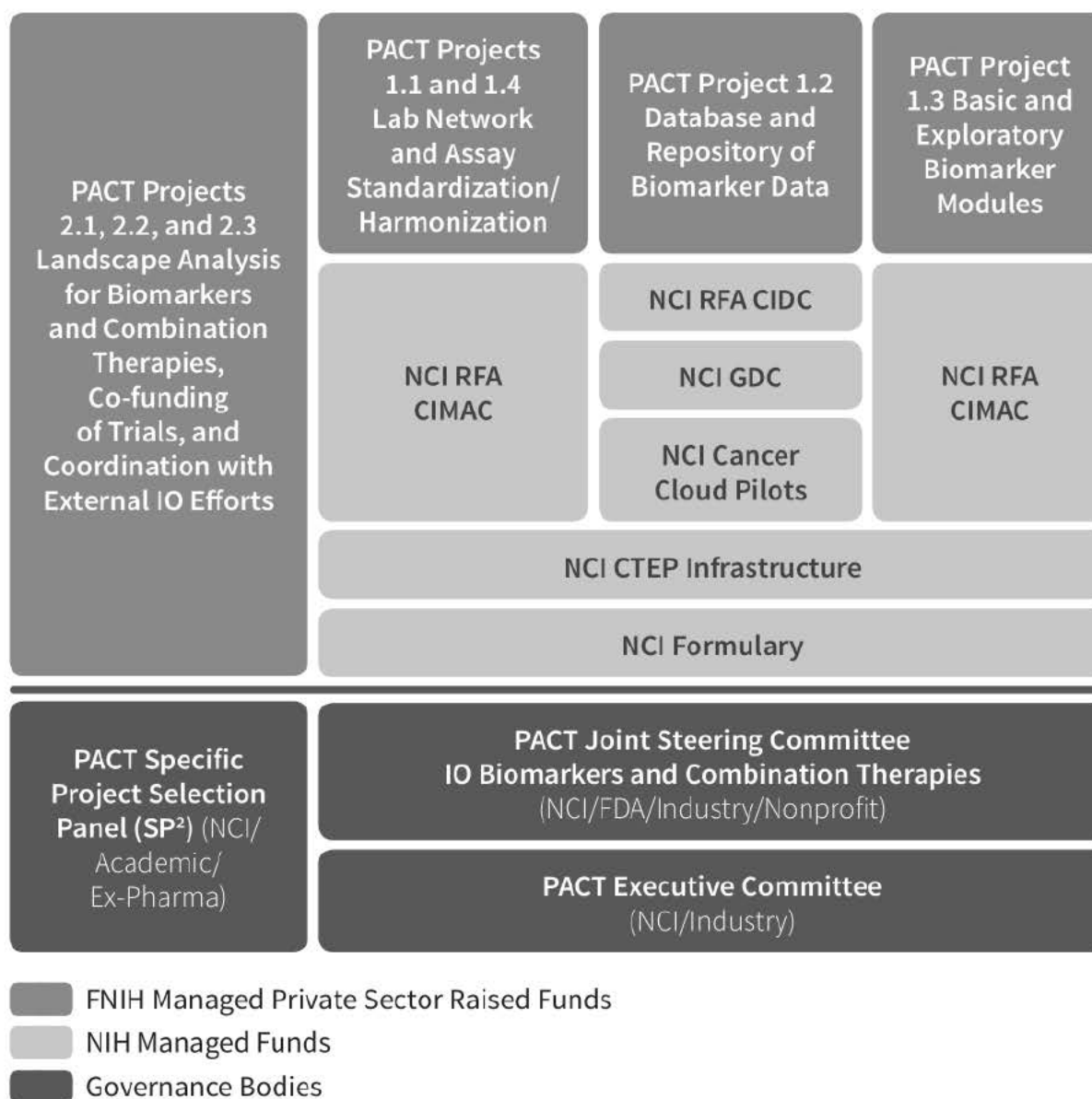
(b) (4)

The following summarizes the total costs to support Program Area 2:

Program Area 2 Consolidated Budget

| PROJECT PLAN SECTION | BUDGET ITEM/ PROJECT GOAL | (b) (4) | TOTAL PROJECT COST |
|--|--|---------|--------------------|
| Project 2.1 | Conduct biannual landscape analysis to determine priority biomarkers and combination therapies | (b) (4) | (b) (4) |
| | Compensate SP ² members for trial and biomarker landscape review | | |
| Project 2.2 | Co-fund high-priority combination clinical trials | | |
| Project 2.3 | Conduct outreach and coordinate with other IO efforts | (b) (4) | (b) (4) |
| PROGRAM AREA 2 | | | |
| Further PACT Trial Co-Funding (Optional) ► Additional funding for specific clinical trials and biomarkers, which can be decided on a trial-by-trial basis | | | |

PACT Governance



To achieve its objectives, PACT will require a governance structure that 1) maintains close involvement by both public and private partners in key decisions; 2) protects confidential or proprietary information and guards against conflicts of interest; 3) provides both continuous strategic direction for the partnership and rigorous operational management of its different component parts; and 4) enables timely decision-making, avoiding unnecessary bureaucracy. To accomplish these goals, we propose four **focused governing bodies to run the partnership**:

1. An operationally focused PACT Joint Steering Committee (JSC), each member of which will direct different aspects of the PACT research plan.

2. A PACT Scientific Project Selection Panel (SP²) to analyze existing and potential therapeutic and biomarker studies and make recommendations regarding which biomarker studies could be executed as part of PACT. This will be an advisory rather than decision-making body. The JSC will make the actual selection of which trials should be part of PACT based on the SP²'s recommendations.
3. A PACT Executive Committee (EC) to provide high-level strategic direction, communication with the top leadership of each of the partner organizations, and resolution of general policy issues. The EC will oversee the actions of the JSC and the SP² and communicate with other PACT partners via an Extended Executive Group, consisting of senior executives from partner organizations not actively serving on the EC.
4. In addition, a PACT Patient Advisory Committee (PAC) will be added to the governance structure of PACT upon the launch of PACT years 4-5, consisting of representatives from cancer patient advocacy organizations. The PAC will periodically review the progress of PACT and provide input to the EC and JSC on PACT's relevance to and support of cancer patient needs and concerns.

PACT Joint Steering Committee (JSC)

Execution of the research programs in PACT will be governed through a JSC composed of members from participating companies, government agencies, and nonprofit organizations. The JSC will operate under the direction of the PACT Executive Committee (EC).

The responsibilities of the JSC will include:

1. Reviewing the recommendations of the PACT SP² (described below) and using these recommendations to set operational research priorities for PACT programs, including selecting the optimal combination therapy trials for PACT partnerships.
2. Reviewing the progress of projects on an ongoing basis and adjusting project plans to ensure appropriate tradeoffs between the timely achievement of key project milestones and production of quality results. The JSC is therefore the primary forum for discussion among the PACT partners of potential operational changes to the final research plan, based on emerging opportunities and challenges, and within the context of the project budgets.
3. Meeting regularly with the Core Laboratory Committee (CLC) to ensure lab coordination and development and distribution of SOPs and best practices.
4. Conducting assessments of key project milestones, including critical go/no-go milestones, and communicating these assessments to the EC.
5. Determining how private sector funds provided to FNIH are distributed (consistent with the final research plan).
6. Working with the potential PACT PAC, which will be composed of patient advocates.

7. Reviewing the results of the research efforts under PACT and making recommendations regarding how they are disseminated and publicized, consistent with NIH publication rules.
8. Overseeing active outreach to, and coordination with, other related cancer research and trial efforts as described in Project 2.3 (above).

While the final overall research plan for PACT will be decided jointly by NIH/NCI and industry partners, the funds provided by NIH and industry for PACT will flow through separate streams. NIH funds must be disbursed according to NIH procedures for solicitation of applications, review of applications, and decision-making. NIH will have final statutory decision-making authority over the conduct of its grants, as provided in the federal regulations, although private sector partners will have the ability to provide input on the progress of the NIH-funded research through the JSC.

Private sector partner funds will be contributed through and managed by FNIH. (FNIH will also coordinate any material in-kind private sector contributions to PACT.) Such funds may be dispersed directly by FNIH through grants or contracts, or transferred by FNIH to NIH for disbursement through NIH grants. The JSC will review and select proposals made directly to FNIH for funding. After awards are made, the JSC will provide project oversight for all studies, whether funded by NIH or industry/FNIH, in a manner consistent with NIH procedures as described above.

The membership of each of the JSC will be as follows:

- ▶ Three to four NIH members (voting), including program officials for the relevant NIH grants
- ▶ At least one representative from FDA (nonvoting)
- ▶ One voting representative from each funding industry partner; additional industry representatives may attend as alternates but will be nonvoting
- ▶ One voting representative from each nonprofit organization that matches company funding levels for PACT
- ▶ Subject matter experts, such as academic investigators, whether funded by PACT or not; may be added at the JSC's discretion, but will be nonvoting
- ▶ At least one representative from FNIH (ex-officio, nonvoting)

The JSC will be co-chaired by one NIH and one industry representative, selected by the PACT EC, but who is not part of the EC.

After the projects are launched, the JSC will meet regularly (likely monthly) via teleconference, and at least twice yearly in person. The frequency of meetings will be adjusted as the scientific agenda requires. The JSC may also convene smaller “working groups” of experts that include PACT stakeholders to advise on specific areas of science or technical aspects of the research plan. The decisions of the JSC will be made by simple majority. Each participating company will have one vote as will each qualifying nonprofit partner, and the resulting private sector cumulative

vote will remain constant at 50 percent of the total votes. If additional industry members are added to the partnership, votes for all industry participants will be scaled appropriately. NIH will have votes that will not exceed 50 percent of the total. The goal of the JSC will be to drive consensus on partnership decisions. In the unlikely event that this cannot be achieved, any conflicts will be raised to the EC for resolution. JSC operational logistics, staffing, and project management will be managed by FNIH.

PACT Scientific Project Selection Panel (SP²)

Some of the most important decisions made in the course of PACT involve choosing appropriate studies or projects to execute using the PACT infrastructure or with PACT funding. These include consideration of which biomarkers or preclinical models to develop, around which drugs or drug combinations these efforts should be focused, and—for Program Area 1 (biomarkers)—which clinical trials should be selected to have biomarker studies executed in PACT (Program Area 2). We expect that proposals to execute combination clinical trials with biomarker studies defined in the modules within PACT will be of several different types:

1. A proposal for a biomarker “companion study” to be run using an NCI-sponsored (ETCTN or NCTN) trial as a “backbone,” where samples and clinical data collected from such trials are run through the PACT infrastructure.
2. A proposal to test combinations brought to PACT by one or more industry partners, where samples and data collected from these trials would be developed using the PACT core labs.
3. External sponsors of individual trials could also choose to run PACT biomarker modules using PACT-developed assays and standard SOPs in labs they select outside the PACT core labs and contribute data back to the NCI Data Commons.

Evaluating studies that are proposed to run under PACT or which datasets to accept into PACT will require significant scientific expertise, potential access to sensitive or confidential company data (such as proposed trial protocols, results of point of care or early-phase preclinical or clinical studies, investigator brochures), and the ability to provide objective recommendations that are based on the science rather than individual commercial considerations. In this regard, the JSC will need to rely on advice from a separate panel of oncology experts who are knowledgeable about oncology (with a particular focus on IO) and who have practical experience in biomarker and therapeutic development, but can provide objective advice and are free of conflicts of interest with regard to the interests of specific companies. PACT will establish the SP² to fill this advisory role.

The SP² will determine which potential therapeutic combinations and which biomarkers have the highest priority for assessment in the PACT infrastructure. The SP² will oversee the conduct and distribution of the landscape analysis described in Project 2.1 above and will use information from the landscape analysis and other sources to identify candidate studies for PACT. FNIH will provide research services (through a subcontracted consulting group if needed) to collect

the background information needed to assess these studies. FNIH (or its subcontractor) will execute the necessary confidentiality agreements with companies and other entities whose studies are being considered by the SP² and with individual SP² members to ensure proprietary or confidential information is used only to support PACT decisions and is protected from inappropriate disclosure. The SP² will focus on combinations that address currently unmet needs for the field and for patients (i.e., are not effectively being tested elsewhere) and that offer a compelling scientific rationale for inclusion in PACT and make specific recommendations to the JSC about which studies to pursue. The SP² may also communicate its most general findings more broadly where they may be of use to specific sponsors or to the oncology community.

The membership of the SP² should include the following:

- ▶ NCI scientists and medical officers with expertise in PACT interest areas. This may include one or more members of the JSC who can act as liaisons.
- ▶ FDA scientists.
- ▶ Academic researchers with relevant clinical and translational research expertise. These members, while they serve on the panel, will not be able to serve as principal investigators on studies associated with PACT.
- ▶ Scientists with industry experience in oncology drug development who do not have current employment with or active ties to individual companies in the areas of interest for PACT, to avoid conflicts of interest.
- ▶ One or more representatives from nonprofit/patient organizations with an interest in IO.

The SP² will meet at least quarterly (or more often if needed) by teleconference. Two of these quarterly meetings will be set to correspond to the completion of the twice yearly landscape analysis updates. The SP² will be co-chaired by one NIH and one academic researcher and will report to the PACT EC. Each member will have one vote; decisions will be made by simple majority. In the unlikely event that consensus cannot be achieved, conflicts will be raised to the EC for resolution. SP² operational logistics, staffing, and project management will be managed by FNIH.

PACT Executive Committee (EC)

The PACT EC will be responsible for oversight of PACT, ensuring that the partnership overall is conducted efficiently and in the best interests of patients and the public health, and for communicating the value of PACT to its partners and the public. Specifically, the EC will be responsible for the following:

1. Providing general guidance for the overall strategy of PACT within the rapidly changing oncology landscape.

2. Reviewing the progress of PACT on a regular basis and ensuring its effective and timely execution. This includes review and approval of major go/no-go milestones and funding changes.
3. Communicating the progress of PACT and any related challenges to the partners and the oncology community, and managing the relationships among the partners.
4. Establishing the policies that govern PACT and ensuring they are adhered to.
5. Overseeing the operation of the PACT JSC and SP², and resolving any conflicts or questions that they may not be able to resolve on their own.
6. Considering new initiatives or partners that may be added to PACT over time.

The membership of PACT (voting, except where otherwise noted) will include the following:

- ▶ The Director of the National Cancer Institute (or the Director of the Division of Cancer Treatment and Diagnosis) at NCI's discretion
- ▶ The Deputy Director of NCI
- ▶ The Director of CTEP, Division of Cancer Treatment and Diagnosis, NCI
- ▶ Two representatives from FDA (representing both CDER and CDRH)
- ▶ A patient advocate representative
- ▶ Three senior-level executives from three different biopharmaceutical company partners (head of research and development or global head of oncology research or development)
- ▶ A representative from the NIH Office of the Director (ex-officio, nonvoting)

The EC will be co-chaired by one senior official from NCI and one senior executive from one of the industry partners. It will meet at least quarterly by teleconference and will seek opportunities to meet periodically in person as schedules allow. Voting will be by simple majority.

To insure effective communications with and input from all PACT stakeholders, an Extended Executive Group, consisting of the EC members and representatives from the private sector partners not currently included on the EC, will be established to receive regular updates on PACT and advise the EC on its progress and direction. The Extended EC will meet twice a year by teleconference. The EC and the Extended Executive Group will be convened and supported by FNIH.

Consolidated Total Budget Estimate

The following table summarizes the budget inputs from Program Areas 1 and 2 into a single high level view of the total PACT budget:

| CONSOLIDATED ITEMIZED PACT BUDGET | | | | |
|--------------------------------------|---|---------|--------------------------|---------|
| ALL COSTS REFLECT TOTAL OVER 5 YEARS | | | | |
| PROJECT PLAN SECTION | BUDGET ITEM/ PROJECT GOAL | (b) (4) | TOTAL PROJECT COST | (b) (4) |
| Project 1.1.1 and 1.2 | Create core laboratory network to conduct biomarker assays | | \$102M | |

| CONSOLIDATED ITEMIZED PACT BUDGET | | | | |
|--------------------------------------|--|---------|--------------------------|---------|
| ALL COSTS REFLECT TOTAL OVER 5 YEARS | | | | |
| PROJECT PLAN SECTION | BUDGET ITEM/ PROJECT GOAL | (b) (4) | TOTAL PROJECT COST | (b) (4) |
| Project 1.3 | Create database to bank IO biomarker data from clinical trials | | \$40M | |

*Indirects lower for this project because a majority of work will occur at NCI and not academic institutions.

| CONSOLIDATED ITEMIZED PACT BUDGET | | | | |
|--------------------------------------|--|--------------------------|--|---------|
| ALL COSTS REFLECT TOTAL OVER 5 YEARS | | | | |
| PROJECT PLAN SECTION | BUDGET ITEM/ PROJECT GOAL | (b) (4) | | (b) (4) |
| | | TOTAL PROJECT COST | | |
| Project 1.1.2 | Develop new IO biomarkers | \$40M | | |
| Project 1.4 | Standardize and harmonize biomarker assays for IO therapy | \$11.25M | | |

| CONSOLIDATED ITEMIZED PACT BUDGET | | | | | |
|--------------------------------------|--|---------|--|--------------------|---------|
| ALL COSTS REFLECT TOTAL OVER 5 YEARS | | | | | |
| PROJECT PLAN SECTION | BUDGET ITEM/ PROJECT GOAL | (b) (4) | | TOTAL PROJECT COST | (b) (4) |
| Project 1.1.2 and 1.4 | Expand biorepository capabilities for sample storage | | | \$12.5M | |
| PROGRAM AREA 1 | | | | \$205.75M | |
| Project 2.1 | Conduct biannual landscape analysis to determine priority biomarkers and combination therapies | | | \$1.15M | |
| | Compensate SP ² members for trial and biomarker landscape review | | | \$0.5M | |

| CONSOLIDATED ITEMIZED PACT BUDGET | | | | | |
|--------------------------------------|---|---------|--|--------------------|---------|
| ALL COSTS REFLECT TOTAL OVER 5 YEARS | | | | | |
| PROJECT PLAN SECTION | BUDGET ITEM/ PROJECT GOAL | (b) (4) | | TOTAL PROJECT COST | (b) (4) |
| Project 2.2 | Co-fund high-priority combination clinical trials | (b) (4) | | \$27M | (b) (4) |
| Project 2.3 | Conduct outreach and coordinate with other IO efforts | | | | |
| PROGRAM AREA 2 | | (b) (4) | | \$28.65M | (b) (4) |
| FNIH Program Management Costs | | | | \$16.6M | |
| PACT Initiative Total | | (b) (4) | | \$251M | (b) (4) |
| Program Area 1—"Buy-up" Option | | | | | |
| Program Area 2—"Buy-up" Option | | | | | |

Appendices

Appendix 1: Exploratory Biomarker Modules – Detailed Description

Evaluation of unknown biomarkers can be performed depending on availability of samples from the periphery and tissue and specific objectives of the relevant clinical trial. Various stakeholders (e.g., National Cancer Institute or company sponsor) can choose to fund these modules based on specific trial objectives or shared objectives across multiple studies.

Module 1c: Immune Cell Biology

As a potential expansion to the study of the immune cell biology to develop novel biomarkers, the PACT team suggest single-cell sequencing of tumor cells and immune cell subsets on a small number of tumors, such as myeloid-derived suppressor cells (MDSC), tumor-associated macrophages (TAM), neutrophils, T-cell clonality, and the use of newer technologies such as NanoString and CyTOF imaging, can be used to understand immune cell characterization, cell trafficking, and spatial co-localization of multiple cell types in the tumor microenvironment (TME).

Focus of the Project

Tumor and Periphery

- Analyze and compare different immune cell populations in the tumor and periphery (blood) by immunohistochemistry (IHC) and flow cytometry (or CyTOF) with standard operating procedures and quality-controlled experiments. Examples of potential markers are listed in Table A-1.

TABLE A-1: EXAMPLES OF CELL POPULATIONS

CELL POPULATIONS/MARKERS (EXAMPLES)

T cells (e.g., CD3, CD8, CD4, CD45RO, FoxP3, TIM3, LAG3, PD1, etc.)

NK cells (e.g., CD5, CD16, etc.)

B cells (CD19, activation markers, etc.)

Macrophages (e.g., CD163, CD206, CD64, etc.)

Dendritic cells (e.g., CD11c, CD1c, CDC141, HLA-DR, ILT7, etc.)

MDSCs (e.g., OLR1, CD15, CD14, etc.)

Neutrophils

Mast cells

Eosinophils

- ▶ Use similar marker set for flow cytometry and IHC, when possible:
 - ▷ Have multiple methods assessing same markers to ensure quality data.
 - ▷ Flow cytometry allows for quantification of immune cell subsets.
- ▶ IHC allows for analysis of localization of different immune populations (e.g., in T-cell- rich/ poor areas, edge, etc.).
- ▶ Depending on sample size, ability to do multiple panels will allow evaluation/quantification of larger number of markers than IHC. Will need to propose prioritized panels if sample is limiting.
- ▶ Functional cell analysis (e.g., T-cell and MDSC assays).
- ▶ Compare immune cell subsets in blood versus tumor.
- ▶ New assay formats allowing visualization of the 3-dimensional immune architecture of selected larger tumor samples (perhaps from pre-operative trials/window of opportunity trials) could be explored. This would expand knowledge obtained from standard IHC (Gerner, Kastenmuller, Ifrim, Kabat, & Germain, 2012; Gerner, Torabi-Parizi, & Germain, 2015).
 - ▷ Program infrastructure (clinical and bioinformatics) should be established with a view that technology combining assessment of molecular markers in the context of tumor (maybe tumor-draining lymph node as well) spatial architecture will evolve and will need to be incorporated in the future.

Module 2b: Cancer Genetics/Somatic Mutations

There are at least three high-priority expansion biomarkers that should be considered for answering specific questions related to DNA analysis: copy number alterations, single-nucleotide polymorphisms (SNP), and T-cell-receptor (TCR) and B-cell receptor (BCR) deep sequencing. Each of these should be employed as called for in relation to the mechanism of action of the therapy being tested.

Single-Nucleotide Polymorphisms (SNPs)

While still exploratory, germline SNPs that are associated with autoimmune disease may be useful to predict response or adverse events in cancer immunotherapy. One approach is to use SNP arrays to characterize established autoimmune markers. For example, genome-wide association studies have identified hundreds of SNPs associated with autoimmune diseases such as rheumatoid arthritis, lupus, and multiple sclerosis (Gregersen, Diamond, & Plenge, 2012). Immuno-oncology (IO) therapies alter the state of the immune system within the TME, and a major limitation is autoimmune adverse events. SNP genotyping will determine if the genetic predisposition to autoimmune disorders is predictive of response to IO therapy or adverse events. Ninety-five percent of 612 SNPs associated with 21 common autoimmune diseases can be genotyped using a combination of two commercially available SNP chips (MEG and Immune) from Illumina. These chips could be enhanced with additional SNPs associated with less common autoimmune disorders observed as adverse events during IO treatment.

TCR and BCR Deep Sequencing

Advances in genome sequencing technologies have also enabled the development of a new powerful platform for probing the adaptive immune systems (immunosequencing). Millions of TCR or BCR sequences can be read in parallel from a single sample by immunosequencing for the quantification of T- and B-cell clonal response in peripheral blood and tumor. The clinical application of immunosequencing for the diagnosis and monitoring of lymphoid malignancies demonstrated high sensitivity and specificity. The presence of tumor-infiltrated lymphocyte (TIL) correlates with a favorable clinical outcome. Emerging data suggest that both the number of TIL and degree of specific clonal expansions in pretreatment melanoma samples are predictive of response to anti-PD-1 therapy (Tumeh et al., 2014). TCR repertoire in peripheral blood correlates with immune-related adverse events in patients treated with immune checkpoint blockade. Immunosequencing biomarkers have the potential to help guide dose regimens and combination therapies. Moreover, for adoptive T-cell transfer or chimeric antigen receptor T-cell therapy, immunosequencing is used to identify novel tumor antigen/neoantigen-specific TCR and monitor the therapy itself by tracking the injected T cells. Immunosequencing has opened many avenues with the breadth of potential application in immunotherapy.

Module 3b: Transcriptomic Characterization of Microenvironment

Emerging technologies are making significant progress in characterizing the primary and acquired resistance mechanism for patients. Challenges include potential changes in RNA during the formation of single-cell suspensions that are required for current scRNA-seq protocols, low capture efficiency of cellular transcripts (10–15% using 3' poly-A capture), and limited sensitivity that makes detection of low-abundance transcripts unreliable. RNA-seq analysis of single functional cytolytic T cells with various immune phenotype markers provides additional information about the impacts of different molecules on cytolytic function, potentially to explore their correlation with clinical outcome.

Focus of the Project

Single-cell suspensions can be obtained from tumor samples where the tissue is processed with or without enzyme digestion, with a need to establish cell freezing media under a standard operation procedure.

No single marker will serve the purpose of transcriptomic characterization of the TME. Therefore, the main focus should be on comprehensive measurements of multiple baseline and on-therapy markers that are related to response and resistance to IO agents. Some of the currently available readouts include the interferon gamma signature, the cytolysis score, and mesenchymal or stemness tumor phenotype.

Experimental Screening Platforms To Include and Purpose for Each:

- ▶ Whole-transcriptome profiling via next-generation sequencing (NGS) is recommended with baseline profiling at a minimum, and longitudinal samples for tumor indications where available are strongly encouraged.

- ▶ Peripheral blood mononuclear cell profiling is also recommended.
- ▶ Application of emerging single-cell characterization techniques are suggested to be explored and incorporated.

Emerging tissue processing approaches such as those that recover single nuclei for RNA-seq provide an opportunity to characterize immune subpopulations with unprecedented specificity. One advantage of single-cell techniques compared with bulk profiling is that the molecular features of rare subpopulations can be extracted and may help to identify novel targets. Another advantage is that one can clearly assess the relative frequencies of the various subpopulations such as T cells, T-regulatory cells, MDSCs, and TAMs.

In addition to providing an opportunity to characterize specific immune subpopulations within the TME, single-cell profiling can resolve cell subpopulations that are obscured by whole-tissue transcriptome profiling as well as their associated gene expression patterns and dynamics, and quantify cellular heterogeneity within a tissue, peripheral blood, fine-needle aspirate, or bone marrow aspirate.

Value Proposition

It is important to characterize the primary and acquired resistance mechanisms for patients who fail to respond to immune checkpoint blockade monotherapy, or transiently respond and then progress afterward. Transcriptomic profiling is one approach to identify these resistance mechanisms and guide combination clinical strategies, and can also be used to assess the impact of drug treatment to identify or validate pharmacodynamics markers of response.

Module 4b: Liquid Biopsy – Circulating Tumor Cells (CTCs), cfRNA, Exosomes

Focus of the Project

For the expansion biomarker module for liquid biopsy, we will look to develop techniques for better analyzing CTCs, cfRNA, and exosomes.

Experimental Screening Platforms To Include and Purpose for Each:

- ▶ Quantitative polymerase chain reaction (qPCR) – research tool that is readily translatable into commercial and regulatory viable *in vitro* diagnostic
- ▶ NGS – RNA-seq – good for biomarker discovery/research, laboratory-developed test approaches; also may be preferred technology in specific settings (e.g., detection of minimal residual disease in certain heme malignancies)
- ▶ Epic Biosciences and Rarecyte CTC platforms – selection agnostic CTC approaches; broader potential across many tumor types
- ▶ Exosome collection and subsequent DNA/RNA sequencing methods

Module 5: Defining the Role of the Microbiome in Modulating Cancer Immunotherapy Responses

Determinants of response to checkpoint blockade are under intense research and are likely to include immunosuppressive status in the TME as well as systemic priming status of the immune system.

Microbiome biomarker development is an active area of research that has already yielded intriguing results that have not only associated microbial population changes with oral, pancreatic, and colon cancer, but may also yield clues regarding the molecular mechanisms linking microbial interactions with these and other types of tumors (Linares, Gustafsson, Baquero, & Martinez, 2006; Schloissnig et al., 2013).

At present, there are no human datasets linking microbiome changes with anti-tumor responses. However, some intriguing recent preclinical studies suggest that the microbiome is required for the anti-tumor activity of anti-PD-L1 and anti-CTLA4, as these antibodies lack their efficacy in mice devoid of microbiota, and the efficacy is transmissible to poor-responder mice via the microbiota. Although we are at a very early stage in this field, these animal studies suggest that systemic immunity is in part regulated by the microbiome.

Value Proposition

Since human data are fundamental to start to address the role of the microbiome in cancer immunotherapy, we propose to stimulate prospective studies in patients undergoing immunotherapy. The principal activity will focus on bacterial communities measurable in fecal samples. Potentially, this project could be expanded to include multiple microbial communities across different mucosal surfaces.

Microbes as Biomarkers

Well-characterized and validated biomarkers of disease can be used for cancer detection and diagnosis, or to measure patient response to therapeutics, and may also provide a rationale for choice of therapy.

The importance of developing microbiome-based patient phenotypes is supported by recent studies demonstrating that when gut bacterial communities are compromised, immunotherapy and standard chemotherapy regimens may lose efficacy (Iida et al., 2013; Viaud et al., 2013). Thus, a detailed knowledge of each cancer patient's unique microbiome could have high translational value to clinical practice since this information could be exploited for the purposes of optimizing individual therapeutic responses, possibly by altering microbial signals to change host metabolic regulation or by developing new metrics for patient stratification based upon matching therapeutic agents with an individual's microbial metabolism or immune profile.

Focus of the Project

Depending on the clinical application, microbiome-based biomarkers may be developed by examining various features and readouts, alone or in combination with existing biomarkers. For example, advanced *in silico* techniques have been used to analyze individual metagenomic profiles as a molecular biomarker that may identify pathogenic or drug-resistance collective phenotypes (Zackular, Rogers, Ruffin, & Schloss, 2014).

Indeed, a current clinical trial (NCT02141945) is testing a metagenomic-based diagnostic tool for patients with colonic neoplasia.

Other strategies have been devised to associate specific tumor/microbe interactions that include the following:

- ▶ Analysis of whole-organism presence/abundance
- ▶ Detection/quantification of biosynthetic products (outer membrane vesicles, miRNA, toxins, lipopolysaccharide [LPS])
- ▶ Detection/quantification of microbial metabolites (short-chain fatty acids [SCFAs], 2-HG, bile acids)
- ▶ Molecular signatures of host responses to altered microbiomes

Thus, colonic hyperpermeability and pro-inflammatory cytokine profiles that are associated with specific bacterial taxa could be used to identify individuals at risk for disease progression or poor therapeutic response.

Potential biomarkers that PACT could expand to test are:

- ▶ Levels of bacterial taxa (16S sequence data)
- ▶ Levels of bacterial metabolites (SCFAs, bile acids, etc.)
- ▶ Levels of bacterial enzymes (β -glucuronidase (GUS), bile acid hydrolases, etc.)
- ▶ Levels of serum LPS, muramyl dipeptide
- ▶ Host inflammatory cytokines/host molecular signatures of dysbiosis

Experimental Screening Platforms To Include and Purpose for Each:

- ▶ Enzyme activity screens (480-well) for detecting bacterial enzyme levels
- ▶ Microarray or enzyme-linked immunosorbent assay for detecting cytokine profiles
- ▶ High-throughput mass spectrometry for detecting bacterial metabolites
- ▶ Quantitative immunohistochemistry for detecting immune checkpoint receptor levels after probiotic treatment

Module 6: Non-Immune Cell Characterization of Tumor Microenvironment (Differentiation, Stroma, Vasculature, Etc.)

Tumor resistance and immune evasion are influenced tremendously by the surrounding nonimmune microenvironment that can include stromal cells, blood vessels, and small particles (e.g., exosomes, ectosomes, microvesicles), cytokines, and enzyme or adhesive properties that are derived from these. These have distinct roles based upon the type of cancer (solid tumor versus hematologic disseminated tumor) and intrinsic driving tumor biology.

Focus of the Project

PACT could use the following as a starting point for expansion biomarker modules:

- ▶ Small particles (exosomes, ectosomes, microvesicles) from blood and the TME.
- ▶ Antibodies that selectively separate mesenchymal stromal cells from tumor and hematopoietic immune cells and strategies to isolate these for single-cell molecular characterization.
- ▶ Markers of blood vessels (i.e., CD34, CD31 and endoglin), effective angiogenesis, and tumor hypoxia and strategies to accurately quantitate these in relevant models.
- ▶ The representative nonimmune cell genes (DNA and RNA) could be used to assess the signature of vasculature, stroma, and other nonimmune cells in the TME. It is of importance to explore their correlation with tumor and immune cell-derived signature in the same tumor, as well as clinical outcome.
- ▶ Baseline serum vascular endothelial growth factor (VEGF) demonstrated the correlation with clinical outcome in melanoma patients treated with CTLA-4 blockade.
- ▶ Combination anti-VEGF with checkpoint blockade showed better clinical response in patients with melanoma and renal cell carcinoma.

Experimental Screening Platforms To Include and Purpose for Each:

As small particles and their contents will be mixed in blood, technologies that separate these based upon distinct antigens expressed by the releasing nonimmune microenvironment cells will be important.

If canine models of spontaneous cancer are chosen to study this, it will be necessary to establish the reagents compatible with exosome (and other small particle separation) and also IHC and separation strategies for other types of stromal cells.

Imaging strategies that allow examination of intracellular exosomes and their trafficking along with adhesive properties of tumor and stromal cells will be important.

Support of a comprehensive center to study this in the setting of spontaneous canine tumors or another large animal model will be needed.

Value Proposition

While features related to tumor vasculature and angiogenesis have been extensively studied and therapeutics directed toward this successfully, our understanding of the other components of the nonimmune microenvironment is at an elemental stage. Furthermore, animal models available to study this are very limited. An opportunity to study these interactions comes potentially from the many solid and hematologic spontaneous mouse models and also companion canine models of cancer where serial sampling of tumors can occur and sufficient blood volume can be obtained to study soluble factors as well. Early clinical data showed that combination immune checkpoint blockade with the agents to overcome nonimmune-cell-derived suppression potentially achieved a synergistic, favorable clinical response.

Appendix 2: Additional Assay Standardization and Harmonization Examples

PDL-1 IHC Comparability Example

An example of a collaboration that addresses comparability of assay approaches across multiple immunohistochemistry (IHC)-based PD-L1 tests is the Blueprint PD-L1 IHC Assay Comparison Project developed by four pharmaceutical companies (Bristol-Myers Squibb, Merck & Co. Inc., AstraZeneca PLC, and Genentech, Inc.) and two diagnostic companies (Agilent Technologies, Inc./Dako Corp and Roche/ Ventana Medical Systems, Inc.) in collaboration with the International Association for the Study of Lung Cancer and the American Association for Cancer Research (AACR). The project aims to cross compare four different diagnostics, including U.S. Food and Drug Administration (FDA)-approved tests, for detection of PD-L1 expression in tumor tissue (Averbuch et al., 2015). The PD-L1 IHC 22C3 pharmDx test was approved as a companion diagnostic to pembrolizumab as a single agent in second-line nonsmall-cell lung cancer (NSCLC). The test was used to determine patient eligibility in a single arm study KEYNOTE 001. The PD-L1 IHC 28-8 pharmDx test was approved by the FDA as a complementary test to another PD-1 inhibitor, nivolumab, in the nonsquamous nonsmall-cell lung cancer (NSCLC) and melanoma patient populations. The scope of the Blueprint Project was to establish technical comparability between the assays. Preliminary results of this effort were presented at the 2016 AACR annual meeting. Analyses from the Blueprint Project confirm that there is high concordance for the two approved PD-L1 diagnostics in NSCLC (American Association for Cancer Research, 2016; Hirsch et al., 2017).

Assay Harmonization Effort Examples

Currently, there are several ongoing initiatives to coordinate and harmonize immunoprofiling efforts including the Human Immunology Project, Minimal Information About T Cell Assays (MIATA), human leukocyte antigen-peptide multimer assays, and others (Britten et al., 2009; Britten et al., 2012; Maecker et al., 2010; Maecker, McCoy, & Nussenblatt, 2012; Mandruzzato et al., 2016).

Other technologies, such as gene expression microarrays, have achieved a reasonable degree of standardization led by consortia such as the Microarray Quality Control (Patterson et al., 2006), the External RNA Controls Consortium (Devonshire, Elaswarapu, & Foy, 2010), and the EMERALD project (Beisvåg et al., 2011).

Another example of assay harmonization to minimize data variability and allow worldwide correlations is the Immunoscore initiative (Galon et al., 2012). Effective large-scale assay harmonization efforts have been conducted for IHC-based immunological assays of immune cell populations in formalin-fixed paraffin-embedded (FFPE) tumor sections. The Immunoscore includes the immune cell density, calculated by numerical quantification of two lymphocyte populations, cytotoxic and memory T cells at the tumor center, and the invasive margin of tumors. This criterion has the potential to establish prognosis of patient clinical outcome,

regardless of the absence of other cancer-associated prognostic markers, such as in early tumor stage (I/II) patients. Importantly, it will need to be validated as a predictor of response for immunotherapy.

Pre-analytical Considerations for Standardization of Key Assays

Pre-analytical processing of samples for diagnostic assays including those used for single-cell immune response assays, such as ELISpot or flow cytometric analysis, includes patient-related factors such as tissue-ischemia time, pretreatment with drugs, dynamic nature of the analyte, and sample heterogeneity. Analyte stability can be affected by the sample collection process including anticoagulants and preservatives used for blood draws, freezing/thawing conditions, time between collection and testing, and storage conditions before processing (Mallone et al., 2011).

IHC, the most widely used platform for biomarker assessment in diagnostic surgical pathology and for retrospective research, is a multistep process that requires standardized conditions for tissue collection, fixation and processing, preparation of the IHC slide, and interpretation of the staining results. IHC-based assays remain important tests as complementary diagnostics and companion diagnostics to assess antigen expression on diagnostic or surgical specimens for selecting patients for specific targeted therapies (e.g., HER2 expression for Herceptin), and more recently PD-L1 measurement as a companion diagnostic for pembrolizumab treatment of NSCLC patients. Published guidelines for measuring established biomarkers such as estrogen receptor, progesterone receptor, and HER2 are available (Hammond et al., 2010). General guidelines, including analyte stability and laboratory quality control, for performing analysis of tissue-based molecular biomarkers have been published (Cree et al., 2014).

Next-generation sequencing tests for tumor mutation analysis, similar to other complex molecular diagnostic tests, should demonstrate adequate analytical performance. It should follow standard operating procedures that specifically address materials and procedures including patient's sample type, method of nucleic acid extraction, as well as technical metrics for nucleic acid quantification and quality, which can negatively impact on sensitivity and reproducibility of the assay (Pant, Weiner, & Marton, 2014; Rehm et al., 2013).

The preparation of intact and pure mRNA is one of the key factors in mRNA gene quantification using gene expression profiling of RNA sequencing. Extraction of nucleic acids and particularly RNA is very sensitive to nucleases. Thus, nuclease free conditions should be implemented to control variability in steps such as sample collection, tissue fixation, and FFPE block handling including sectioning. For the extraction of nucleic acids from the FFPE tumor tissue, a method for the simultaneous isolation of high-quality DNA, RNA, and microRNA as well as protein from the same sample has been developed (Kalmar et al., 2013).

Appendix 3: The PACT Design Team

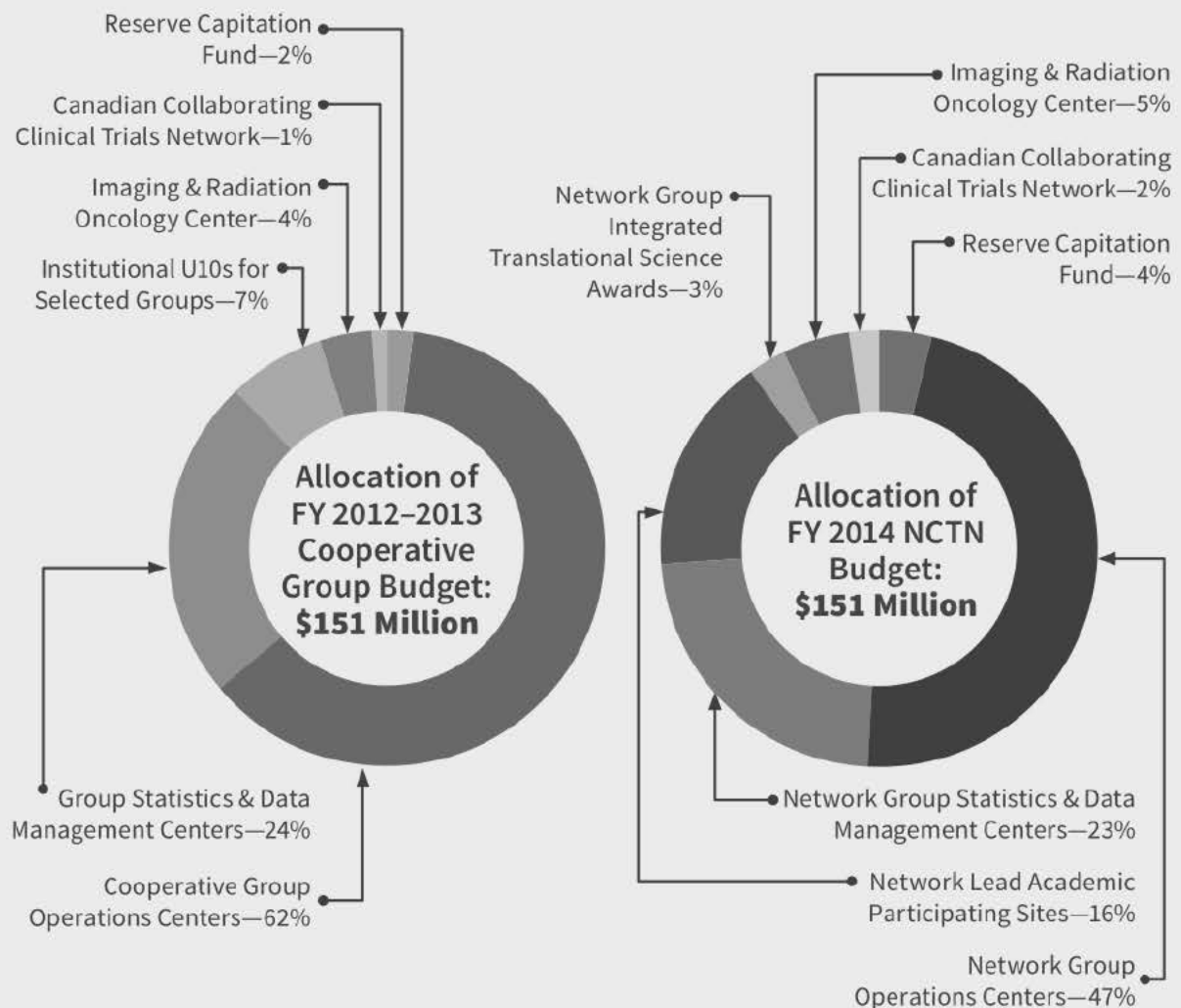
| INDUSTRY PARTICIPANTS | Jeff Engelman (Novartis)—Industry Co-Chair | | Axel Hoos (GSK)—Industry Co-Chair | |
|-------------------------|--|-----------------------------|-----------------------------------|----------------------------|
| | Bob Abraham (Pfizer) | Matthew Albert (Genentech) | Carl Barrett (AstraZeneca) | Olaf Christensen (EMD) |
| | Ute Dugan (BMS) | Jeff Ecsedy (Takeda) | Jessie English (EMD) | Howard Fingert (Takeda) |
| | Vicki Goodman (BMS) | Thomas J. Hudson (AbbVie) | Norbert Kraut (B-I) | Stuart Lutzker (Genentech) |
| | Greg Plowman (Lilly) | Chandra Ramanathan (Bayer) | David Reese (Amgen) | Paul Rejto (Pfizer) |
| | Andrew Schade (Lilly) | Armin Schuler (EMD) | Flavio Solca (B-I) | Jianda Yuan (Merck) |
| GOVERNMENT PARTICIPANTS | Helen Chen (NCI)—NIH Co-Chair | | Percy Ivy (NCI)—NIH Co-Chair | |
| | Rebecca Baker (NIH) | Gideon Blumenthal (FDA) | Kevin Howcroft (NCI) | Tony Kerlavage (NCI) |
| | Allison Lea (NIH) | Ke Liu (FDA) | Lisa McShane (NCI) | Reena Phillip (FDA) |
| | Larry Rubenstein (NCI) | Malcolm Smith (NCI) | Howard Streicher (NCI) | Marc Theoret (FDA) |
| | Magdalene Thurin (NCI) | | | |
| ACADEMIC PARTICIPANTS | John Byrd (OSU) | Levi Garraway (Broad/Lilly) | Steve Hodi (DFCI) | Patricia LoRusso (Yale) |
| | Antoni Ribas (UCLA) | Lillian Siu (PMCC) | Mario Sznol (Yale) | Jedd Wolchok (MSKCC) |
| PACT PROGRAM MANAGEMENT | Stacey Adam (FNIH) | David Wholley (FNIH) | | |

Appendix 4: Detailed Description of the Cancer Therapy Evaluation Program (CTEP) – National Clinical Trials Network (NCTN)

The NCTN Budget

The overall NCTN budget for these awards is \$151 million. This amount is the same as the total budget provided to the Cooperative Groups for awards in each of fiscal years (FY) 2012 and 2013, despite the substantial reductions in the National Cancer Institute (NCI) budget that resulted from sequestration starting in 2013. What has changed, however, is the distribution of funds to the various components of the NCTN, as compared with the components of the former Cooperative Group program.

The distribution of funds to the Network Group Operations Center grants changed from 62 percent in FY 2012 and 2013 to 47 percent in FY 2014 due to the consolidation of the infrastructures of the Operations and Statistical Centers; funding of new components in the NCTN, including the Lead Academic Participating Sites and Integrated Translational Science Awards; and expansion of the Imaging and Radiology Oncology Group for the entire network. The new system provides for an annual enrollment of about 17,000 patients on interventional trials, a 15 percent reduction compared with about 21,000 enrolled patients in recent years. This reduction is anticipated to occur gradually over 2 to 3 years. To this end, NCI reserved funds to distribute to the NCTN groups later in FY 2014 to accommodate an enrollment of about 21,000 patients.

COMPARISON OF COOPERATIVE GROUP PROGRAM FUNDING AND NCTN PROGRAM FUNDING

Funding Precision Medicine Trials

NCI believes that reducing the budget of the Network Group Operations Centers will not impede the NCTN's ability to perform important trials. Conducting the new generation of clinical trials requires new technologies and procedures, including tissue collection (fresh biopsy samples are often necessary), advanced DNA and RNA sequencing methods with rapid turnaround times, and complex analytic algorithms to distinguish normal genetic variants from tumor-specific changes. These, in turn, entail new expenses for surgery, interventional radiology, molecular pathology, and bioinformatics that have not typically been a part of clinical trials.

However, although the screening tests may need to be performed on very large numbers of patients to find those whose tumors exhibit the appropriate molecular profile, the numbers of patients required for interventional studies are likely to be smaller than what was required in previous trials.

That is because the patient selection is based on having the target for the new therapy, leading to larger differences in clinical benefit (such as how long patients live overall or live without tumor progression) between the intervention and control groups. Thus, future clinical trials will, in many cases, require fewer numbers of patients due to the selection of patients most likely to benefit from the intervention being tested.

Although screening patients for tumors with specific molecular characteristics may require large numbers of patients, the screening components of studies are less costly than the actual interventional study. Hence, clinical trials in the future are likely to involve screening components, which will be reimbursed at a lower rate, with smaller interventional components that will be reimbursed at higher rates. More precision in patient selection will permit study designs that can aim for larger therapeutic effects and thereby further decrease the size of trials.

Efficiencies in Collaboration

These changes will, however, require the NCTN groups to function differently compared with how they functioned in the previous system. For example, NCTN groups should be able to reduce the costs of conducting trials by sharing resources. If a particular group has many active trials, it may have to decrease the number of new trials it is planning. Groups with fewer active trials can take up those new trials instead. This collaborative approach should allow members of one NCTN group to support trials led by other groups and should afford NCTN members an ability to conduct a full portfolio of trials in the most common cancers.

Because the NCTN has only four U.S. adult groups, with fewer Operations and Statistical Centers that require financial support, some savings are anticipated. This consolidation was planned for over the past several years, and NCI provided \$24 million in funding supplements to the newly consolidated groups to help them absorb the costs of their ongoing trials as well as to fund the integration of their separate infrastructures.

NCI also provided more than \$40 million in other funding supplements to transition all the groups to a common data management system (Medidata Rave®), develop an integrated IT system for the tissue banks, and implement specific precision medicine clinical trials.

Additional Support

For the past several years, NCI has provided significant additional annual support for the Cooperative Groups and will continue to provide these funds for the NCTN, in addition to the grant funding described above. Clinical trials are complex undertakings that require a host of support organizations and funding streams. The new system includes a number of other features that are not included in the NCTN awards but are essential to carrying out the NCTN mission.

The additional support includes:

- Central Institutional Review Boards, an important component of NCI's clinical trials system that has added speed, efficiency, and uniformity to ethics review.

- ▶ The Cancer Trials Support Unit, an NCI-funded contract that provides clinical investigators and their staff with one-stop online access to NCTN trials and allows investigators to register new patients.
- ▶ A dedicated tissue bank for each Network group funded through a separate NCI award mechanism.
- ▶ The Biomarker, Imaging, and Quality of Life Studies Funding Program, a separate funding stream for NCTN trials that supports correlative science studies on group trials. NCTN groups compete for funds that are specifically reserved annually for this purpose. The availability of dedicated funds greatly facilitates coordination as clinical trials must meet stringent deadlines.
- ▶ In addition, approximately one-quarter of patient accrual on NCTN treatment trials is paid for by the NCI Community Oncology Research Program (NCORP; previously the Community Clinical Oncology Program/Minority-Based Community Clinical Oncology Program). The community hospitals and medical centers participating in the NCORP are reimbursed for accruing patients to NCTN treatment trials by their NCORP awards, not via the NCTN Group Operations award.

| ADDITIONAL ANNUAL NCI SUPPORT | |
|---|---------------|
| NCI Central IRBs (Adult & Pediatrics) | \$4.5 Million |
| Cancer Trials Support Unit | \$14.0 |
| Tissue Banks | \$8.6 |
| Biomarker, Imaging, and Quality of Life Studies Funding Program | \$10.0 |
| NCORP Support for NCTN Treatment Trials (Estimated) | \$33.1 |
| \$70.2 Million* | |

Other NCI support includes but is not limited to:

- ▶ Operations of common data management system (Medidata Rave®)
- ▶ Clinical trials auditing
- ▶ Drug storage and distribution
- ▶ Regulatory oversight (CTEP IND Studies)

*This is an approximation and is dependent on annual NCI appropriations.

Finally, in addition to these substantial annual expenditures, NCI also subsidizes the NCTN by paying for many other essential clinical trial functions, thereby further reducing costs borne by the Network groups:

- ▶ NCI will pay for the licenses and hosting fees of the electronic, common data management system, called Medidata Rave®, used by all NCTN groups.
- ▶ NCI will oversee a national audit system for NCTN trials.
- ▶ NCI will manage Investigational New Drug applications to the U.S. Food and Drug Administration along with the distribution of these drugs for many NCTN trials.

It is estimated that support for these activities costs NCI approximately \$15 million annually.

<https://www.cancer.gov/research/areas/clinical-trials/nctn/budget>

Appendix 5: Active NIH/NCI Requests for Applications (RFAs) Relevant to PACT

2017

1. CA17-009 Mechanisms of Cancer Drug Resistance and Sensitivity (U54)
2. CA17-006 Cancer Immunologic Data Commons (CIDC) (U24)
3. CA17-005 Cancer Immune Monitoring and Analysis Centers (U24)
4. CA17-013 Advanced Development and Validation of Emerging Biospecimen Science Technologies for Basic and Clinical Cancer Research (R33)

2016

5. CA16-501 Limited Competition: Cancer Immunotherapy Trials Network (CITN)(UM1)

References

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From: Wholley, David (FNIH) [T]
Sent: Wed, 20 Dec 2017 20:56:08 +0000
To: Koroshetz, Walter (NIH/NINDS) [E]
Cc: Baker, Rebecca (NIH/OD) [E]; Porter, Linda (NIH/NINDS) [E]; Porter, Linda (NIH/NINDS) [E]; Volkow, Nora (NIH/NIDA) [E]; Stein, Jack (NIH/NIDA) [E]; Collins, Francis (NIH/OD) [E]; Tabak, Lawrence (NIH/OD) [E]; Wolinetz, Carrie (NIH/OD) [E]; Biarnes, Michael (FNIH) [T]; Menetski, Joseph (FNIH) [T]
Subject: FW: FAST TURNAROUND REVIEW: Opioid PPP update for BMAC 12-19-17 draft for NIH
Attachments: Opioid PPP update for BMAC 12-19-17 draft rb2 fsc.docx

Walter,

Thanks for taking the time to review this and make changes. I think your changes on page 2 to reorder and tighten up the Asset and Data Section and Biomarkers and Endpoints are really very helpful. My only concern would be your edits to the "Strategic Research Goals" up front— this is copied pretty closely from the last document sent to PhRMA, and I would be concerned that changing too much of the language there makes it look like we are "moving the goalposts." I would rather we kept that section as is and address the changes needed in the Progress Update section.

Since Nora and Larry sent their changes in a separate document I will address those in a separate email.
Thanks, David

From: Koroshetz, Walter (NIH/NINDS) [E]
Sent: Wednesday, December 20, 2017 12:41 PM
To: Baker, Rebecca (NIH/OD) [E] (b) (6); Porter, Linda (NIH/NINDS) [E] (b) (6); Volkow, Nora (NIH/NIDA) [E] (b) (6); Stein, Jack (NIH/NIDA) [E] (b) (6)
Cc: Collins, Francis (NIH/OD) [E] (b) (6); Wolinetz, Carrie (NIH/OD) [E] (b) (6); Tabak, Lawrence (NIH/OD) [E] (b) (6); Wholley, David (FNIH) [T] <dwholley@fnih.org>; Biarnes, Michael (FNIH) [T] <mbiarnes@fnih.org>
Subject: RE: FAST TURNAROUND REVIEW: Opioid PPP update for BMAC 12-19-17 draft for NIH

Thanks Rebecca. I took a quick look and added edits. If doesn't go out tonight let me know and I can relook. Booked solid til 9PM.

Walter

From: Baker, Rebecca (NIH/OD) [E]
Sent: Wednesday, December 20, 2017 8:39 AM
To: Koroshetz, Walter (NIH/NINDS) [E] (b) (6); Porter, Linda (NIH/NINDS) [E] (b) (6); Volkow, Nora (NIH/NIDA) [E] (b) (6); Stein, Jack (NIH/NIDA) [E] (b) (6)
Cc: Collins, Francis (NIH/OD) [E] (b) (6); Wolinetz, Carrie (NIH/OD) [E] (b) (6); Tabak, Lawrence (NIH/OD) [E] (b) (6); Wholley, David (FNIH) [T] <dwholley@fnih.org>; Biarnes, Michael (FNIH) [T] <mbiarnes@fnih.org>
Subject: FAST TURNAROUND REVIEW: Opioid PPP update for BMAC 12-19-17 draft for NIH

Good morning,

As follow up to last week's partnership design meeting, FNIH has drafted the attached summary to share with the PhRMA Biomedical Advisory Council.

PhRMA has asked for a draft by COB today. Could you please review and send your revisions and edits by 4 PM today? Please be sure to copy David and Mike.

Thank in advance for your thoughts,

Rebecca

From: Wholley, David (FNIH) [T]

Sent: Tuesday, December 19, 2017 7:38 PM

To: Collins, Francis (NIH/OD) [E] (b) (6)

Cc: Baker, Rebecca (NIH/OD) [E] (b) (6); Menetski, Joseph (FNIH) [T]

<jmenetski@fnihi.org>; Biarnes, Michael (FNIH) [T] <mbiarnes@fnihi.org>

Subject: Opioid PPP update for BMAC 12-19-17 draft for NIH

Francis – Please see my draft of the summary of our progress on the opioid initiative that Bill Chin requested in advance of the January 4 BMAC meeting. He asked for two pages; however given his introductory and closing sections are a page long in themselves my draft result is three pages, but does let them know we've come up with specific conclusions. Feel free to suggest changes to shorten it further of course. I have yet to add the page summarizing AMP and PACT that he requested as this took most of the effort.

(b) (4)

Rebecca, I leave to you whether you think we should simply distribute this more broadly at this point (to Nora, Jack, Walter, etc) or whether you think Francis will want to/have time to make changes first. Bill asked for a final draft by cob tomorrow.

Thanks, David

From: Wholley, David (FNIH) [T]
Sent: Mon, 27 Nov 2017 16:52:42 +0000
To: Collins, Francis (NIH/OD) [E]
Cc: Volkow, Nora (NIH/NIDA) [E]; Koroshetz, Walter (NIH/NINDS) [E]; Stein, Jack (NIH/NIDA) [E]; Wolinetz, Carrie (NIH/OD) [E]; Porter, Linda (NIH/NINDS) [E]; Tabak, Lawrence (NIH/OD) [E]; Baker, Rebecca (NIH/OD) [E]; Biarnes, Michael (FNIH) [T]; Menetski, Joseph (FNIH) [T]
Subject: FW: FDA Meeting on December 11-12

Please see below. I think we stick to our original plan of kicking this off with focus area 1 on the morning of day 1 (12th), then going to pain on that afternoon of day 1 and continuing the discussion the following day (13th). We can include the key conclusions from focus area 1 discussion in the sum-up at the end of day 2 (of course). Let me know what you think.

From: Hertz, Sharon H [REDACTED] (b) (6)
Sent: Monday, November 27, 2017 11:30 AM
To: Wholley, David (FNIH) [T] <dwholley@fnih.org>
Cc: Biarnes, Michael (FNIH) [T] <mbiarnes@fnih.org>; Menetski, Joseph (FNIH) [T] <jmenetski@fnih.org>
Subject: RE: FDA Meeting on December 11-12

Thanks, that is a great idea except Ellen will be covering the division while I am at the FDA meeting. I understand that it is difficult to move meetings with so many people.

I don't think you need to change the agenda for the meeting. Both areas are important, so I'll just have to miss whichever is on the 12th.

Sharon

Sharon Hertz, MD
Division Director
DAAAP
[REDACTED] (b) (6)

From: Wholley, David (FNIH) [T] [mailto:dwholley@fnih.org]
Sent: Monday, November 27, 2017 11:18 AM
To: Hertz, Sharon H [REDACTED] (b) (6)
Cc: Biarnes, Michael C (NIH) <mbiarnes@fnih.org>; Menetski, Joseph M (NIH) <jmenetski@fnih.org>
Subject: RE: FDA Meeting on December 11-12

What if we did pain on the 12th and delayed focus area 1 (addiction and overdose) discussions to the morning of day 2 (the 13th). Am assuming someone like Ellen Fields might be able to make both the 12th and 13th, and provide some continuity. Would that work?

From: Hertz, Sharon H [REDACTED] (b) (6)
Sent: Monday, November 27, 2017 9:17 AM

To: Wholley, David (FNIH) [T] <dwholley@fnih.org>

Cc: Biarnes, Michael (FNIH) [T] <mbiarnes@fnih.org>; Menetski, Joseph (FNIH) [T] <jmenetski@fnih.org>

Subject: RE: FDA Meeting on December 11-12

It is some of the companies. I don't know if it is the same people or not, but there are many issues that could impact the drug and device companies so we expect many to attend. Beyond that, many of us at FDA are conflicted. For example, Doug Throckmorton and I are speaking/moderating on the 12th. We can have people cover, but I'm sure you understand that it is very difficult to have continuity from us if different people attend meetings on the same topic.

Sharon

Sharon Hertz, MD

Division Director

DAAAP

(b) (6)

From: Wholley, David (FNIH) [T] [mailto:dwholley@fnih.org]

Sent: Sunday, November 26, 2017 1:09 PM

To: Hertz, Sharon H (b) (6)

Cc: Biarnes, Michael C (NIH) <mbiarnes@fnih.org>; Menetski, Joseph M (NIH) <jmenetski@fnih.org>

Subject: FDA Meeting on December 11-12

Hi Sharon—

On one of our opioid partnership calls last week you brought up a concern that our face to face meeting scheduled for December 12-13 will conflict with a meeting FDA is planning to hold on Dec 11-12. I did speak to NIH leadership about this and they are concerned there are other conflicts, making moving the dates of the 12-13th meeting. In looking up the FDA meeting on the Federal Register, I notice it is specifically to discuss Packaging, Storing, and Disposal Options to Enhance Opioid Safety. Given this I am not sure of the degree of overlap with our planned meeting. I can see where some of the same companies would attend both meetings, but do you anticipate it will be the same actual personnel from those companies? And would the conflicts apply equally to the representatives and companies attending the current pain focus area discussions, or is it mainly a concern with respect to the companies associated with the addiction and overdose focus area currently led by NIDA? If the latter, though not optimal we could consider arranging the agenda for the 12-13 to put the addiction and overdose discussions on the second day. Please let me know. David

We've moved! Please find our new address below.

David Wholley

Director, Research Partnerships

Foundation for the National Institutes of Health

(301) 594-6343

fnih.org

11400 Rockville Pike Suite 600 North Bethesda, MD 20852

Learn more about the FNIH in our **2016 Annual Report**: fnih.org/AnnualReport.

From: Wholley, David (FNIH) [T]
Sent: Mon, 13 Feb 2017 21:48:42 -0500
To: Baker, Rebecca (NIH/OD) [E]; Lea, Allison (NIH/OD) [E]
Cc: Collins, Francis (NIH/OD) [E]; Tabak, Lawrence (NIH/OD) [E]; Lowy, Douglas (NIH/NCI) [E]; Doroshow, James (NIH/NCI) [E]; Abrams, Jeff (NIH/NCI) [E]; Adam, Stacey (FNIH) [T]; Melencio, Cheryl (FNIH) [T]
Subject: FW: Final draft of PACT white paper
Attachments: New PACT WP 021117.docx, PACT Implementation Phase Outreach - 1st Round 021317.pptx

Sorry, hit the send button too soon. Copying Rebecca and Allison on this as well. David

From: Wholley, David (FNIH) [T]
Sent: Monday, February 13, 2017 9:47 PM
To: Collins, Francis (NIH/OD) [E] (b) (6); Lowy, Douglas (NIH/NCI) [E] (b) (6); Tabak, Lawrence (NIH/OD) [E] (b) (6); Doroshow, James (NIH/NCI) [E] (b) (6); Abrams, Jeff (NIH/NCI) [E] (b) (6)>
Cc: Adam, Stacey (FNIH) [T] <sadam@fnih.org>; Melencio, Cheryl (FNIH) [T] <cmelencio@fnih.org>
Subject: Final draft of PACT white paper

Dear Francis, Doug, Larry, Jim, and Jeff,

I hope this note finds you all well. As promised, I am sending you the final draft of the PACT white paper for your review. It is still going through a final copy edit and layout, but has been fully reviewed and vetted by our NCI, FDA, and company PACT team members; all of them agree this version of the document reflects the consensus of the group and is ready for circulation to you.

I would ask that you please return any final feedback or edits you may have to Stacey Adam and me by COB Thursday (February 16) if possible. Because the final formatting of the document is being done simultaneously with your review, we should be able to incorporate any final edits swiftly. Our goal is to get the final document to the companies and other stakeholders by the end of this week if possible so we can begin formal fundraising. (b) (4), (b) (5)

(b) (4), (b) (5)

Thank you all for the time and the support you have provided to us during this process and for the excellent work your teams have contributed to the draft alongside our company and academic partners. Please let me know if there is anything you'd like to discuss further upon reviewing this. I will be in (b) (6) for the AMP RA/SLE meeting beginning Wednesday, but can make myself available by phone if needed.

Thanks,
David

From: Wholley, David (FNIH) [T]
Sent: Fri, 24 Feb 2017 16:54:39 -0500
To: Collins, Francis (NIH/OD) [E]
Cc: Wood, Gretchen (NIH/OD) [E]; Baker, Rebecca (NIH/OD) [E]; NIHDirectorMeetings; Adam, Stacey (FNIH) [T]
Subject: FW: Final draft of PACT white paper
Attachments: New PACT WP 02-20-17 Clean.docx

Hi Francis:

I just wanted to remind you that we'd sent you the final draft PACT document for review and ask that if you have any changes to suggest you get them back to Stacey and me by Monday noon. We want to keep our promise to get this final version officially "out" to the companies in February. Thanks, David

From: Adam, Stacey (FNIH) [T]
Sent: Monday, February 20, 2017 5:12 PM
To: Wholley, David (FNIH) [T] <dwholley@fnih.org>; Collins, Francis (NIH/OD) [E] (b) (6)
Lowy, Douglas (NIH/NCI) [E] (b) (6); Tabak, Lawrence (NIH/OD) [E]
(b) (6); Doroshov, James (NIH/NCI) [E] (b) (6); Abrams, Jeff
(NIH/NCI) [E] (b) (6)
Cc: Melencio, Cheryl (FNIH) [T] <cmelencio@fnih.org>; Baker, Rebecca (NIH/OD) [E]
(b) (6); Lea, Allison (NIH/OD) [E] (b) (6)
Subject: RE: Final draft of PACT white paper

Dear NIH and NCI Colleagues,

As promised in my email last night, I am circulating a new draft of the whitepaper with a number of edits made.

Again, if you have already started your review on the other draft we sent, that is no problem. I will be able to still incorporate your edits into this new draft. If you have not yet started your review, I would recommend reviewing this new draft.

Please do not hesitate to reach out if you have any questions. We look forward to receiving your feedback early this week.

Thank you again for your assistance in this effort.
Stacey

Stacey J. Adam, Ph.D.
Scientific Program Manager, Cancer
Foundation for the National Institutes of Health
Direct (301) 435-8364 | Mobile (b) (6)

From: Adam, Stacey (FNIH) [T]
Sent: Sunday, February 19, 2017 9:21 PM
To: Wholley, David (FNIH) [T] <dwholley@fnih.org>; Collins, Francis (NIH/OD) [E] (b) (6)
Lowy, Douglas (NIH/NCI) [E] (b) (6); Tabak, Lawrence (NIH/OD) [E]

(b) (6); Doroshow, James (NIH/NCI) [E] <(b) (6)>; Abrams, Jeff (NIH/NCI) [E] (b) (6)
Cc: Melencio, Cheryl (FNIH) [T] <cmelencio@fnih.org>
Subject: RE: Final draft of PACT white paper

Dear NIH and NCI Colleagues,

I hope you all are having a lovely long weekend and you are getting some well-earned rest. I wanted to reach out and remind you that the draft we provided last week for the PACT whitepaper was to be copy edited and one-voiced simultaneously with your review.

To that end, if you have begun reviewing the draft that was sent, I would ask that you not spend a lot of time on wordsmithing as we have just received copy edits from our writing team and they have done quite a thorough review. However, if you have not begun review of the draft yet, and would like to hold off, I should be circulating a new draft tomorrow with all of their revisions and a others that I have received.

No matter which draft you review, I will be sure to incorporate you suggested changes. We appreciate you taking the time to review the draft and provide us with any feedback that you may have.

Thanks,
Stacey

Stacey J. Adam, Ph.D.
Scientific Program Manager, Cancer
Foundation for the National Institutes of Health
Direct (301) 435-8364 | Mobile (b) (6)

From: Wholley, David (FNIH) [T]
Sent: Monday, February 13, 2017 9:47 PM
To: Collins, Francis (NIH/OD) [E] (b) (6); Lowy, Douglas (NIH/NCI) [E] (b) (6); Tabak, Lawrence (NIH/OD) [E] (b) (6); Doroshow, James (NIH/NCI) [E] (b) (6); Abrams, Jeff (NIH/NCI) [E] (b) (6)
Cc: Adam, Stacey (FNIH) [T] <sadam@fnih.org>; Melencio, Cheryl (FNIH) [T] <cmelencio@fnih.org>
Subject: Final draft of PACT white paper

Dear Francis, Doug, Larry, Jim, and Jeff,

I hope this note finds you all well. As promised, I am sending you the final draft of the PACT white paper for your review. It is still going through a final copy edit and layout, but has been fully reviewed and vetted by our NCI, FDA, and company PACT team members; all of them agree this version of the document reflects the consensus of the group and is ready for circulation to you.

I would ask that you please return any final feedback or edits you may have to Stacey Adam and me by COB Thursday (February 16) if possible. Because the final formatting of the document is being done simultaneously with your review, we should be able to incorporate any final edits swiftly. Our goal is to get the final document to the companies and other stakeholders by the end of this week if possible so we can begin formal fundraising. (b) (4), (b) (5)

Thank you all for the time and the support you have provided to us during this process and for the excellent work your teams have contributed to the draft alongside our company and academic partners. Please let me know if there is anything you'd like to discuss further upon reviewing this. I will be in (b) (6) for the AMP RA/SLE meeting beginning Wednesday, but can make myself available by phone if needed.

Thanks,
David

From: Wholley, David (FNIH) [T]
Sent: Wed, 26 Apr 2017 20:02:05 -0400
To: Collins, Francis (NIH/OD) [E]; Lowy, Douglas (NIH/NCI) [E]; Doroshow, James (NIH/NCI) [E]
Cc: Baker, Rebecca (NIH/OD) [E]; Adam, Stacey (FNIH) [T]
Subject: FW: Follow-up to Request for PACT Funding
Attachments: image001.png, image002.jpg

Francis, Doug, and Jim:

As promised I got the follow-up notes out today, and below is Mikael Dolsten's response. As you can see, he is still onto his idea expressed several weeks back of breaking PACT into optional modules that different pharma could bid on separately (b) (5)

Hi Mikael:

Thanks for your insights and suggestions. The PACT plan is in fact already somewhat modular, although given that PACT is a partnership in one disease area with a fairly unitary focus it is not quite the same as AMP, where we ended up addressing a general area of R&D challenge (target identification and validation) across three very different disease areas using what turned out to be in fact 3-4 pretty distinct scientific approaches.

To answer your question, our sense on one hand is that there are three "modules" in PACT, as follows, with approximate current estimated cost:

(b) (4), (b) (5)

Module 3 seems clearly separable from the first two, particularly the co-funding of clinical trials, which could potentially be handled outside PACT on a case by case basis if cost is a concern. On the other hand, separating modules 1 and 2 would be substantially more problematic. Almost all of the 14 companies involved in the design felt that the new biomarker piece (module 2) is where the most value lies, but that this value would very difficult if not impossible to realize without also investing substantially in the underlying infrastructure (module (b) (5)

(b) (5)

(b) (5)

Regards,
David

From: Dolsten, Mikael [mailto:Mikael.Dolsten@pfizer.com]
Sent: Wednesday, April 26, 2017 4:35 PM
To: Wholley, David (FNIH) [T] <dwholley@fnih.org>
Cc: Abraham, Robert <Robert.Abraham@pfizer.com>; Rejto, Paul <paul.rejto@pfizer.com>; Adam, Stacey (FNIH) [T] <sadam@fnih.org>; Donnelly, Meredith (FNIH) [T] <mdonnelly@fnih.org>
Subject: Re: Follow-up to Request for PACT Funding

David

I think we expressed at HEVER a preference to consider to participate in specific sub-modules , similar to AMP, rather than entire program . This would offer more alignment w our focus and also mitigate funding levels pending breadth of your interest

Do you foresee PACT able to delineate 2-3 modules ?

Sent from my iPhone

On Apr 26, 2017, at 4:18 PM, Wholley, David (FNIH) [T] <dwholley@fnih.org> wrote:

Dear Bob, Paul, and Mikael,

We are reaching out to follow-up on the PACT Initiative funding request detailed in the email chain below. We know that Mikael attended the HEVER meeting where PACT was discussed, and have heard that overall reception of the effort at HEVER was very positive. We understand that companies have requested some time to discuss the outcome of the meeting internally, but just wanted to follow up to see if you have any further questions and to understand your view of the next steps in the process for Pfizer.

If you would like to meet to discuss, please let Stacey Adam (sadam@fnih.org) know with whom we should work to get something scheduled.

Please also let us know if you have any questions that you need addressed prior to the call, and we will be glad to answer as best we can via email.

Thanks,

David Wholley and Stacey Adam

From: Melencio, Cheryl (FNIH) [T] **On Behalf Of** Wholley, David (FNIH) [T]
Sent: Wednesday, March 22, 2017 11:36 AM
To: 'robert.abraham@pfizer.com' <robert.abraham@pfizer.com>; 'paul.rejto@pfizer.com' <paul.rejto@pfizer.com>; Dolsten, Mikael <mikael.dolsten@pfizer.com>
Cc: Adam, Stacey (FNIH) [T] <sadam@fnihi.org>; Wholley, David (FNIH) [T] <dwholley@fnihi.org>; Donnelly, Meredith (FNIH) [T] <mdonnelly@fnihi.org>
Subject: FW: Partnership for Accelerating Cancer Therapies (PACT) - Final Research White Paper and Funding Request

Dear Bob, Paul, and Mikael,

I hope this note finds you well. I wanted to follow-up on the email that I originally sent to you below on March 1, 2017, as we have not yet heard from your team. Please let us know if you have any questions or require any additional information to assist in your deliberations about the PACT initiative.

If a quick discussion would aid your consideration of this effort, we would be happy to arrange a teleconference. Please just provide us with the names of the individuals we should work with to organize. If you would rather meet in person and will be attending AACR, Stacey Adam and I are available to meet in DC during the meeting between April 2nd at 4pm and April 4th in the early afternoon. We have a few meetings scheduled with other members of PACT already, but can be flexible.

I have attached the PACT whitepaper, executive summary, and briefing slides again for your easy access and reference.

Thank you again for the time and effort you have contributed to PACT thus far. We look forward to hearing from you.

Best,
David Wholley

From: Melencio, Cheryl (FNIH) [T] **On Behalf Of** Wholley, David (FNIH) [T]
Sent: Wednesday, March 01, 2017 9:19 AM
To: 'robert.abraham@pfizer.com' <robert.abraham@pfizer.com>; 'paul.rejto@pfizer.com' <paul.rejto@pfizer.com>; Dolsten, Mikael <mikael.dolsten@pfizer.com>
Cc: Adam, Stacey (FNIH) [T] <sadam@fnihi.org>; Donnelly, Meredith (FNIH) [T] <mdonnelly@fnihi.org>; Wholley, David (FNIH) [T] <dwholley@fnihi.org>
Subject: Partnership for Accelerating Cancer Therapies (PACT) - Final Research White Paper and Funding Request

Dear Bob, Paul, and Mikael,

I am reaching out on behalf of FNIH and the PACT Design Team to thank you for your participation in the Design Phase for the Partnership for Accelerating Cancer Therapies. We are pleased to be able to now

provide you with the final design whitepaper that your company members and the rest of the PACT Design Team have so worked so hard to create.

You will recall that this white paper was assembled following discussions that your company that began last summer about a new Cancer Moonshot-related public-private partnership (PPP) that the NIH/NCI was interested in forming to address some of the challenges facing the development of immunotherapies and related combination therapies in oncology.

We hope you will feel as our PACT team did that the initial research plan laid out in the white paper addresses these challenges both effectively and efficiently, making the most of investments and expertise available from both public and private sector partners. We are now asking that private sector partners consider investing alongside NIH to provide the matching financial funds needed over the next five years to support PACT. In addition to the white paper, we have included a set of PowerPoint slides and a short executive summary to help in your internal decision-making process.

We would like to set up a call at your earliest convenience to discuss this project and our request for your company's continued support. Please let myself (dwholley@fnihi.org) and Stacey Adam (sadam@fnihi.org) know whom we should work with to arrange this discussion.

Once again, thank you for all the hard work that your company member dedicated to this effort already. It has been a pleasure working with Bob and Paul. And thank you for your consideration of our request for your continued financial participation in the project.

Sincerely,
David Wholley

Director of Research Partnerships

Foundation for the National Institutes of Health

9650 Rockville Pike | Bethesda, MD 20814 | www.fnihi.org

<image001.png>

For 13 consecutive years, Charity Navigator has rated the FNIH as an organization that *exceeds industry standards*.

Cheryl Melencio

Executive Assistant, Research Partnerships

Foundation for the National Institutes of Health

9650 Rockville Pike | Bethesda, MD 20814 | www.fnihi.org

Direct (301) 402-4970 | Fax (301) 480-2752

Combined Federal Campaign (CFC) #29165

For 13 consecutive years, Charity Navigator has rated the FNIH as an organization that *exceeds industry standards*.

<image002.jpg>

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Foundation for the
National Institutes of Health

From: Wholley, David (FNIH) [T]
Sent: Fri, 1 Dec 2017 14:03:20 +0000
To: Collins, Francis (NIH/OD) [E]
Subject: FW: GSK representative at AMP Extended Executive Committee Meeting

fyi

From: Patrick Vallance [mailto:patrick.5.vallance@gsk.com]
Sent: Friday, December 1, 2017 8:51 AM
To: Wholley, David (FNIH) [T] <dwholley@fnihi.org>; John Lepore <john.j.lepore@gsk.com>
Cc: Melencio, Cheryl (FNIH) [T] <cmelencio@fnihi.org>
Subject: RE: GSK representative at AMP Extended Executive Committee Meeting

David

Thanks for your note and congratulations. John Lepore will join for GSK and will provide the continuity

Best wishes

Patrick

Ps Not sure that the US has seen the last of me just yet!

From: Wholley, David (FNIH) [T] [mailto:dwholley@fnihi.org]
Sent: 29 November 2017 21:55
To: Patrick Vallance <patrick.5.vallance@gsk.com>
Cc: Melencio, Cheryl (FNIH) [T] <cmelencio@fnihi.org>
Subject: GSK representative at AMP Extended Executive Committee Meeting

EXTERNAL

Dear Patrick:

First of all, congratulations on your new role in the UK beginning next year. You will be sorely missed over here.

I understand (in all senses of the term) you have declined the invitation to attend the AMP EEC call on December 15, and know that Lon Cardon has left GSK. Can you please suggest someone who should replace you and Lon on the EEC, or at least attend this call to represent GSK? Cheryl Melencio can follow up with a revised Outlook indication.

Thanks again, and best of luck
David Wholley

We've moved! Please find our new address below.
David Wholley

Director, Research Partnerships
Foundation for the National Institutes of Health
(301) 594-6343

fnih.org

11400 Rockville Pike Suite 600 North Bethesda, MD 20852

Learn more about the FNIH in our 2016 Annual Report: fnih.org/AnnualReport.

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From: Wholley, David (FNIH) [T]
Sent: Mon, 13 Feb 2017 21:46:58 -0500
To: Collins, Francis (NIH/OD) [E]; Lowy, Douglas (NIH/NCI) [E]; Tabak, Lawrence (NIH/OD) [E]; Doroshow, James (NIH/NCI) [E]; Abrams, Jeff (NIH/NCI) [E]
Cc: Adam, Stacey (FNIH) [T]; Melencio, Cheryl (FNIH) [T]
Subject: Final draft of PACT white paper
Attachments: New PACT WP 021117.docx, PACT Implementation Phase Outreach - 1st Round 021317.pptx

Dear Francis, Doug, Larry, Jim, and Jeff,

I hope this note finds you all well. As promised, I am sending you the final draft of the PACT white paper for your review. It is still going through a final copy edit and layout, but has been fully reviewed and vetted by our NCI, FDA, and company PACT team members; all of them agree this version of the document reflects the consensus of the group and is ready for circulation to you.

I would ask that you please return any final feedback or edits you may have to Stacey Adam and me by COB Thursday (February 16) if possible. Because the final formatting of the document is being done simultaneously with your review, we should be able to incorporate any final edits swiftly. Our goal is to get the final document to the companies and other stakeholders by the end of this week if possible so we can begin formal fundraising. (b) (4), (b) (5)

(b) (4), (b) (5)

Thank you all for the time and the support you have provided to us during this process and for the excellent work your teams have contributed to the draft alongside our company and academic partners. Please let me know if there is anything you'd like to discuss further upon reviewing this. I will be in (b) (6) for the AMP RA/SLE meeting beginning Wednesday, but can make myself available by phone if needed.

Thanks,
David

From: Wholley, David (FNIH) [T]
Sent: Thu, 6 Apr 2017 15:14:31 -0400
To: Collins, Francis (NIH/OD) [E]; Doroshow, James (NIH/NCI) [E]
Cc: Lowy, Douglas (NIH/NCI) [E]
Subject: Final notes for HEVER
Attachments: PACT Outreach Update 040617-FC.docx, Summary of responses to FNIH PACT asks as of 4-5-17.docx
Importance: High

Hi Francis and Jim:

Here is the revised final status grid for PACT, updated to reflect my and Stacey's conversation with Mike Severino and Tom Hudson this morning (put them in the plus column). (b) (4), (b) (5)

(b) (4), (b) (5)

With this, and my reply to Francis's email about the HEVER "respondent" questions sent last night, you should have everything you need. I will let you know any late breaking information by email. I will also check my Blackberry over the weekend from time to time; you can also reach me on my cell at (b) (6)

if anything comes up. Good luck, and let us know anything else we can do to support you.

David

From: Wholley, David (FNIH) [T]
Sent: Thu, 21 Dec 2017 17:12:34 +0000
To: Chin, Bill (Chin@phrma.org)
Cc: Collins, Francis (NIH/OD) [E]; Baker, Rebecca (NIH/OD) [E]
Subject: FNIH PPP Update for BMAC final draft 12-20-17
Attachments: FNIH PPP Update for BMAC final draft 12-20-17.docx

Bill – sorry for the slight delay, had some computer trouble at the time I needed it least, but all resolved. Please see the progress summary you requested for the BMAC of the opioid partnership, which has been reviewed by our NIH colleagues. It may be a bit longer than you wanted, but I preserved your opening and closing sections from your earlier document (governance modified to fit our discussions at the face to face) which take up about page in themselves.

I have also included the additional updates you requested on PACT and AMP. These should be easy to shorten if you need to as you can pretty much drop the bullets and partner lists from each section if desired.

Hope this works for you. Please let me know anything else you may need.

David

From: Wholley, David (FNIH) [T]
Sent: Thu, 16 Mar 2017 20:11:10 -0400
To: Collins, Francis (NIH/OD) [E]; Tabak, Lawrence (NIH/OD) [E]; Dolsten, Mikael; Jan Lundberg
Subject: Further thoughts on replacing Francis Cuss on the AMP Executive Committee

Dear Francis, Larry, Jan, and Mikael:

As you know, Francis Cuss has stepped down from BMS as CSO and has been replaced by Tom Lynch. In advance of HEVER we are trying to come to some agreement about whom we might approach to replace him on the AMP EC, and in what priority. Thank you for the input you have provided thus far.

(b) (4), (b) (5)

(b) (4), (b) (5)

As a next step, could I ask that you weigh in (perhaps by ranking them in your preferred order and adding any comments you may have) and copy the others on this email? Responses are of course confidential among this group. This should help us arrive at a rough consensus. Thank you for taking the time to share your thoughts.

David Wholley

From: Wholley, David (FNIH) [T]
Sent: Wed, 15 Mar 2017 10:51:50 -0400
To: Collins, Francis (NIH/OD) [E]
Subject: FW: [EXTERNAL] Replacement for Francis Cuss

Francis, here is Jan's reply.

(b) (4), (b) (5)

(b) (4), (b) (5)

(b) (4), (b) (5)

Let me know anything else I can do.

David

From: Jan Lundberg [mailto:lundberg_jan@lilly.com]
Sent: Monday, March 13, 2017 4:19 PM
To: Wholley, David (FNIH) [T] <dwholley@fnihi.org>
Subject: Re: [EXTERNAL] Replacement for Francis Cuss

David, the pharma roles at this level has turn over with sometimes unfortunate and unpredictable timings. In relation to replacing Cuss I have the following general suggestions without mentioning specific names: It should be from a company that has if possible involvement in at least one and preferably two of the AMP programs. It may also be good to have someone that has been appointed to the CSO role relatively recently to have some chance of continuity. Finally to have a US based company may help in the current political environment.

(b) (4), (b) (5)

(b) (4), (b) (5)

Best
Jan

Sent from my iPhone

On Mar 10, 2017, at 2:22 PM, Wholley, David (FNIH) [T] <dwholley@fnihi.org> wrote:

Dear Jan:

As I'm sure you've heard, Francis Cuss has stepped down as CSO of BMS. In discussing this with Francis Collins, we agree that we will need to elect a senior industry R&D executive to replace him on the AMP Executive Committee from among the companies not currently represented (AbbVie, Biogen, BMS, GSK, Janssen, Merck, Sanofi, Takeda), but also to have someone in mind that we think would be best suited to the role and be willing to give some time to it--although we've done a good job of trimming back our required meeting schedule I think. Do you have any thoughts about whom we should think about approaching? HEVER is coming up and it would be good to have some idea(s) before then.

Please let me know. Happy to discuss by phone as well, involve others, etc. as you wish.
Regards,
David

From: Wholley, David (FNIH) [T]
Sent: Wed, 15 Mar 2017 10:30:20 -0400
To: Collins, Francis (NIH/OD) [E]
Subject: FW: 2016_12_16_AMP EEC teleconference draft (003) final clean
Attachments: AMP functional downstream opportunities (b) (4).pdf

Hi Francis, just received this from Lon, as follow up to the EEC call on December 16. How would you like this to be handled? Our next EC call is not until May 5. Finding a common date to meet before then would be, as you know, a challenge, though we certainly could try. One solution could be that I send this out to the EC and the SC co-chairs and ask for them to send comments. We'd be asking the EC members for general comments on feasibility and preference on how to proceed; the SC co-chairs would hopefully provide some perspective on how these might be applied in their respective disease area. I would collate comments, and you, Mikael, and Jan could then take this with you to HEVER for further discussion. Please let me know how you'd like to proceed. Thanks, David

From: Lon Cardon [mailto:lon.r.cardon@gsk.com]
Sent: Tuesday, March 14, 2017 10:02 PM
To: Wholley, David (FNIH) [T] <dwholley@fni.h.org>
Cc: Patrick Vallance <patrick.5.vallance@gsk.com>
Subject: RE: 2016_12_16_AMP EEC teleconference draft (003) final clean

Hi David,
Just following up on the prompt below. Patrick Vallance and I have drafted a brief summary to initiate the conversation. It is attached.
Kind regards,
Lon

From: Wholley, David (FNIH) [T] [mailto:dwholley@fni.h.org]
Sent: Tuesday, February 21, 2017 4:53 PM
To: Lon Cardon
Subject: 2016_12_16_AMP EEC teleconference draft (003) final clean

Dear Lon—

(b) (5)

(b) (5) I was reminded of this on a call with Francis today and wanted to reach out to ask if you would be able to write something up fairly soon, as the EC will only have one or at most two more meetings before the Extended EC gets back together. I have attached the meeting minutes from the Dec. 16 call, with your comment highlighted in yellow, for convenience in recalling the context. Please let me know if you think this will be possible sometime in the next couple of weeks—appreciate you are likely extremely busy.

Regards,

David Wholley
Director, Research Partnerships
Foundation for the National Institutes of Health

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From: Wholley, David (FNIH) [T]
Sent: Thu, 7 Dec 2017 00:20:53 +0000
To: Stein, Jack (NIH/NIDA) [E];Chin, Bill (Chin@phrma.org);Baker, Rebecca (NIH/OD) [E]
Cc: Collins, Francis (NIH/OD) [E];Volkow, Nora (NIH/NIDA) [E];Koroshetz, Walter (NIH/NINDS) [E];Porter, Linda (NIH/NINDS) [E];Tabak, Lawrence (NIH/OD) [E];Wolinetz, Carrie (NIH/OD) [E]
Subject: FW: Opioids F2F Meeting Attendees to Date
Attachments: Opioid F2F Attendee List as of 06Dec2017 (4PM).xls

All – for your information (and Jack, in at least two cases, your requested action), please see where we are as of 4PM today on ACCEPTED invitations to next week's face to face meeting. We are at ~65 planned attendees, out of a total ~118 INVITED. We will no doubt get more confirmations before Monday. Based on Mike Biarnes's reckoning, the following is the list of companies that have yet to confirm that at least one of their members will attend. I have added the names of those who have been invited and notes on status as well as action. Let us know if we have missed any company in particular or if you feel you can be of additional help.

(b) (4)

From: Wholley, David (FNIH) [T]
Sent: Thu, 5 Oct 2017 14:53:23 +0000
To: Collins, Francis (NIH/OD) [E]
Cc: Adam, Stacey (FNIH) [T]
Subject: FW: PACT

Further confirmation. I will write jeff back shortly. Sounds like it will be good for Novartis to have a fairly prominent role in governance—we can discuss this with Jim.

David Wholley
Director, Research Partnerships
Foundation for the National Institutes of Health
(301) 594-6343
fnih.org

Learn more about the FNIH in our 2016 Annual Report: fnih.org/AnnualReport.

From: Engelman, Jeffrey [mailto:jeffrey.engelman@novartis.com]
Sent: Thursday, October 05, 2017 10:03 AM
To: Wholley, David (FNIH) [T] <dwholley@fnih.org>
Subject: FW: PACT

Hi David,

Please see below. We had a lot of internal discussion and you can see that we would like to officially participate as outlined in the email below.

I am very pleased that we will be able to help get this launched!

Perhaps we can touch base next week to discuss next steps

Jeff

Jeffrey Engelman, M.D., Ph.D.
Global Head of Oncology
Novartis Institutes for BioMedical Research

Executive Assistant: Anita Caulfield
anita.caulfield@novartis.com
(617)-871-8200

From: "Bradner, James" <james.bradner@novartis.com>
Date: Thursday, October 5, 2017 at 9:58 AM
To: "Collins, Francis (NIH/OD) [E]" (b) (6)

Cc: "Rammohan, Revathi" <revathi.rammohan@novartis.com>, "Brown, Scott" <scott.brown@novartis.com>, Jeffrey Engelman <jeffrey.engelman@novartis.com>, "Hammerman, Peter" <peter.hammerman@novartis.com>, "Dranoff, Glenn" <glenn.dranoff@novartis.com>, Lilli Petruzzelli <lilli.petruzzelli@novartis.com>, "Lockwood, Jeffrey" <jeffrey.lockwood@novartis.com>

Subject: PACT

francis.

thank you for the invitation to steer and now join the NIH-PACT program focused on cancer immunotherapy biomarker discovery. this week we assembled our cancer and institutional leadership (many cc'd here), to examine the clarified design principles emerging from the workstream and to assess alignment with our critical path in IO and cancer medicine. we applaud the effort to pull together so many leading institutions and scientists around this generational activity. we agree violently that the development of next-generation IO agents will require new measurements guiding use and explaining (in)activity. in this regard, we are well aligned with the program and would like to participate.

my sense is that there are important strategic details still to define, regarding scientific focus, institutions/scientific leaders involved, clarified and prioritized measurements. jeff, peter, glenn and lilli cc'd will surely have helpful guidance, should the PACT welcome insights at this pivotal stage. candidly, our principal interest remains connected to the safe harbor the PACT might provide for combination clinical trials of next-gen agents between companies. we would welcome a chance to work with peer institutions through the NIH network. but even with a focus on biomarker creation, curation and deployment, we are motivated to join. i defer to jeff to provide guidance as to how best and who best to contribute these and other guidance.

(b) (4)

finally, we are working hard to help you hit your deadline on the announcement and would like to be a party to the announcement. peter can join in DC at the national press club, if this invitation is still open and helpful.

thank you for the invitation, again, to join. we so admire the heroic work you continue to lead, orienting our government around this rarified moment in biomedicine, openly assembling diverse research communities, and always defending basic research.

please advise on next steps.

best - jay

--

Jay Bradner, M.D.

President | Novartis Institutes for BioMedical Research

james.bradner[at]novartis.com

From: Wholley, David (FNIH) [T]
Sent: Tue, 28 Feb 2017 09:05:05 -0500
To: Collins, Francis (NIH/OD) [E]
Cc: PStoffe4@its.jnj.com; Azanell2@its.jnj.com; Freire, Maria (FNIH) [T]
Subject: FW: PACT and HEVER

Dear Francis:

I provided our Board with an update on our progress on PACT yesterday afternoon. While on the call Paul Stoffels at Janssen mentioned that he is heading up HEVER this year and thinks it might be a good idea to put PACT on the agenda for the April meeting, using the occasion as a forum to encourage other pharma (including those outside of the design effort) to come on board. I mentioned you'd expressed a similar interest and thought it would be good to put you two in contact to insure cross-communication and facilitate getting something on the meeting calendar. I will be happy of course to provide materials, etc as we get closer to the date for the meeting. Please let me know if I can assist otherwise in any way.

Thanks, David

From: Wholley, David (FNIH) [T]
Sent: Fri, 29 Sep 2017 13:35:34 +0000
To: Collins, Francis (NIH/OD) [E]
Cc: Adam, Stacey (FNIH) [T]; Baker, Rebecca (NIH/OD) [E]; Wolinetz, Carrie (NIH/OD) [E]
Subject: FW: PACT and Novartis

Francis, fyi here is the response I sent to Engelman.

David Wholley
Director, Research Partnerships
Foundation for the National Institutes of Health
(301) 594-6343
fnih.org

Learn more about the FNIH in our 2016 Annual Report: fnih.org/AnnualReport.

From: Wholley, David (FNIH) [T]
Sent: Friday, September 29, 2017 9:08 AM
To: 'Engelman, Jeffrey' <jeffrey.engelman@novartis.com>
Cc: Caulfield, Anita <anita.caulfield@novartis.com>
Subject: RE: PACT and Novartis

Hi Jeff:

(b) (4)

It would be great if you could find a way to do the same, and join the group at the announcement on the 12th. Let me know if there is anything I can do to help that process.

David

David Wholley
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Foundation for the National Institutes of Health
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From: Engelman, Jeffrey [<mailto:jeffrey.engelman@novartis.com>]
Sent: Thursday, September 28, 2017 9:20 PM
To: Wholley, David (FNIH) [T] <dwholley@fnih.org>
Cc: Caulfield, Anita <anita.caulfield@novartis.com>
Subject: Re: PACT and Novartis

Hi David,

I hope all is well. As you know, we are very supportive of this concept, and I am personally quite pleased that it is moving forward. (b) (4)

(b) (4)

All the best,

Jeff

Jeffrey Engelman, M.D., Ph.D.
Global Head of Oncology
Novartis Institutes for BioMedical Research

Executive Assistant: Anita Caulfield
anita.caulfield@novartis.com
(617)-871-8200

From: "Wholley, David (FNIH) [T]" <dwholley@fnih.org>
Date: Tuesday, September 26, 2017 at 5:40 PM
To: Jeffrey Engelman <jeffrey.engelman@novartis.com>
Cc: "Caulfield, Anita" <anita.caulfield@novartis.com>
Subject: FW: PACT and Novartis

Hi Jeff:

The announcement of the launch of the Partnership to Advance Cancer Therapies (PACT) is almost certainly going to be on October 12, at the National Press Club. I am being asked by the NIH communications team whom to include in the announcement and related press push, etc. It would be great to have a formal decision from Novartis on PACT as soon as possible. (b) (4)

(b) (4)

Thanks,

David

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Director, Research Partnerships
Foundation for the National Institutes of Health
(301) 594-6343
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From: Bradner, James [<mailto:james.bradner@novartis.com>]
Sent: Tuesday, September 19, 2017 3:23 AM
To: Wholley, David (FNIH) [T] <dwholley@fnihi.org>
Subject: Re: PACT and Novartis

thank you, david. i know that jeff is meeting with (b) (4) this week to discuss. thanks so much - jay

--

Jay Bradner, M.D.
President | Novartis Institutes for BioMedical Research
james.bradner@novartis.com

From: "Wholley, David (FNIH) [T]" <dwholley@fnihi.org>
Date: Monday, September 11, 2017 at 3:48 AM
To: James Bradner <james.bradner@novartis.com>, "Collins, Francis (NIH/OD) [E]"
(b) (6)
Cc: "Jeff, Dana + Lexi Engelman" <jeffrey.engelman@novartis.com>, Scott Brown

<scott.brown@novartis.com>, Revathi Rammohan <revathi.rammohan@novartis.com>

Subject: Re: PACT and Novartis

Hi Jay,

(b) (4)

(b) (4) Please let us know if there are any questions remaining to be answered and we will be happy to jump on the phone.

Regards,
David Wholley
Foundation for the NIH
Sent from my BlackBerry 10 smartphone.

From: Bradner, James
Sent: Sunday, September 10, 2017 9:55 AM
To: Collins, Francis (NIH/OD) [E]
Cc: Wholley, David (FNIH) [T]; Engelman, Jeffrey; Brown, Scott; Rammohan, Revathi
Subject: Re: PACT and Novartis

Thank you, Francis.

(b) (4)

(b) (4)

--

Jay Bradner, M.D.
President | Novartis Institutes for BioMedical Research
james.bradner[at]novartis.com

From: "Collins, Francis (NIH/OD) [E]" (b) (6)

Date: Saturday, September 9, 2017 at 5:08 PM

To: James Bradner <james.bradner@novartis.com>

Cc: "Wholley, David (FNIH) [T]" <dwholley@fnih.org>

Subject: PACT and Novartis

Hi Jay,

(b) (4)



Many thanks, Francis

From: Wholley, David (FNIH) [T]
Sent: Fri, 29 Sep 2017 14:31:32 +0000
To: Collins, Francis (NIH/OD) [E]
Cc: Adam, Stacey (FNIH) [T]; Baker, Rebecca (NIH/OD) [E]; Wolinetz, Carrie (NIH/OD) [E]
Subject: FW: PACT and Novartis

See below. Let's hope

(b) (4)

David Wholley
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From: Engelman, Jeffrey [mailto:jeffrey.engelman@novartis.com]
Sent: Friday, September 29, 2017 10:28 AM
To: Wholley, David (FNIH) [T] <dwholley@fnih.org>
Cc: Caulfield, Anita <anita.caulfield@novartis.com>
Subject: Re: PACT and Novartis

Hi David,

(b) (4)

All the best,

Jeff

Sent from my iPhone

On Sep 29, 2017, at 10:08 PM, Wholley, David (FNIH) [T] <dwholley@fnih.org> wrote:

Hi Jeff:

(b) (4)

It would be great if you could find a way to do the same, and join the group at the announcement on the 12th. Let me know if there is anything I can do to help that process.

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Executive Assistant: Anita Caulfield
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David

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Cc: "Jeff, Dana + Lexi Engelman" <jeffrey.engelman@novartis.com>, Scott Brown <scott.brown@novartis.com>, Revathi Rammohan <revathi.rammohan@novartis.com>

Subject: Re: PACT and Novartis

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(b) (4)

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Regards,

David Wholley

Foundation for the NIH

Sent from my BlackBerry 10 smartphone.

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Sent: Sunday, September 10, 2017 9:55 AM

To: Collins, Francis (NIH/OD) [E]

Cc: Wholley, David (FNIH) [T]; Engelman, Jeffrey; Brown, Scott; Rammohan, Revathi

Subject: Re: PACT and Novartis

Thank you, Francis.

(b) (4)

(b) (4)

(b) (4)

Best -

Jay

--

Jay Bradner, M.D.

President | Novartis Institutes for BioMedical Research

[james.bradner\[at\]novartis.com](mailto:james.bradner[at]novartis.com)

From: "Collins, Francis (NIH/OD) [E]" (b) (6)

Date: Saturday, September 9, 2017 at 5:08 PM

To: James Bradner <james.bradner@novartis.com>

Cc: "Wholley, David (FNIH) [T]" <dwholley@fnih.org>

Subject: PACT and Novartis

Hi Jay,

(b) (4)

Many thanks, Francis

From: Wholley, David (FNIH) [T]
Sent: Mon, 9 Oct 2017 17:57:40 +0000
To: Collins, Francis (NIH/OD) [E]
Cc: Myles, Renate (NIH/OD) [E]
Subject: FW: PACT Press Conference on Oct. 12 at 10:00 am ET

fyi

David Wholley
Director, Research Partnerships
Foundation for the National Institutes of Health
(301) 594-6343
fnih.org

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From: Reese, David [mailto:dreese@amgen.com]
Sent: Monday, October 09, 2017 1:17 PM
To: Myles, Renate (NIH/OD) [E] (b) (6)
Cc: Harper, Sean <sharper@amgen.com>; Coffey, Eva <egroves@amgen.com>; Burklow, John (NIH/OD) [E] (b) (6); Baker, Rebecca (NIH/OD) [E] (b) (6); Wholley, David (FNIH) [T] <dwholley@fnih.org>; Adam, Stacey (FNIH) [T] <sadam@fnih.org>
Subject: Re: PACT Press Conference on Oct. 12 at 10:00 am ET

Renate,

Thanks for the invitation for the press conference. We will try to get a senior person from Amgen there on Thursday - will let you know shortly and once we receive the formal invitation.

Best regards,

Dave

David Reese, MD
Senior Vice President, Translational Sciences
Amgen Inc
+1 805-447-1612

On Oct 9, 2017, at 9:43 AM, Myles, Renate (NIH/OD) [E] (b) (6) wrote:

Hi Drs. Harper and Reese:

David Wholley just shared the exciting news that Amgen will be joining PACT. I did want make you aware that we will be holding a press conference at the National Press Club on Thursday, Oct. 12 at

10:00 a.m. ET to launch this important new partnership. You will be receiving a formal invitation from Dr. Collins to join us. The NPC is located at 529 14th St. NW, Washington, D.C. We have reserved a green room for the entire day (Zenger Room) and will hold a "pre-event" meeting in this room at 9:15 a.m., with the press conference beginning promptly at 10:00 a.m. ET in the Fourth Estate Room.

We hope that an Amgen principal or an appropriate designee will be able to join the event. I will be sharing more specifics about the event tomorrow and will be in touch with Eva shortly about materials.

All the best,
Renate

Renate Myles, MBA

Acting Deputy Director

Office of Communications and Public Liaison

Chief, News Media Branch

National Institutes of Health

Tel: (b) (6)

@RenateMyles

Email: (b) (6)

From: Wholley, David (FNIH) [T]
Sent: Thu, 5 Oct 2017 17:39:35 +0000
To: Doroshow, James (NIH/NCI) [E]; Lowy, Douglas (NIH/NCI) [E]
Cc: Collins, Francis (NIH/OD) [E]; Wolinetz, Carrie (NIH/OD) [E]; Baker, Rebecca (NIH/OD) [E]; Lubenow, Anne (NIH/NCI) [E]
Subject: FW: PACT

Dear Jim and Doug:
Looks like we all landed the big fish. This is now nine companies.

David Wholley
Director, Research Partnerships
Foundation for the National Institutes of Health
(301) 594-6343
fnih.org

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From: Engelman, Jeffrey [mailto:jeffrey.engelman@novartis.com]
Sent: Thursday, October 05, 2017 10:03 AM
To: Wholley, David (FNIH) [T] <dwholley@fnih.org>
Subject: FW: PACT

Hi David,

Please see below. We had a lot of internal discussion and you can see that we would like to officially participate as outlined in the email below.

I am very pleased that we will be able to help get this launched!

Perhaps we can touch base next week to discuss next steps

Jeff

Jeffrey Engelman, M.D., Ph.D.
Global Head of Oncology
Novartis Institutes for BioMedical Research

Executive Assistant: Anita Caulfield
anita.caulfield@novartis.com
(617)-871-8200

From: "Bradner, James" <james.bradner@novartis.com>
Date: Thursday, October 5, 2017 at 9:58 AM
To: "Collins, Francis (NIH/OD) [E]" (b) (6)

Cc: "Rammohan, Revathi" <revathi.rammohan@novartis.com>, "Brown, Scott" <scott.brown@novartis.com>, Jeffrey Engelman <jeffrey.engelman@novartis.com>, "Hammerman, Peter" <peter.hammerman@novartis.com>, "Dranoff, Glenn" <glenn.dranoff@novartis.com>, Lilli Petruzzelli <lilli.petruzzelli@novartis.com>, "Lockwood, Jeffrey" <jeffrey.lockwood@novartis.com>

Subject: PACT

francis.

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thank you for the invitation, again, to join. we so admire the heroic work you continue to lead, orienting our government around this rarified moment in biomedicine, openly assembling diverse research communities, and always defending basic research.

please advise on next steps.

best - jay

--

Jay Bradner, M.D.

President | Novartis Institutes for BioMedical Research

james.bradner[at]novartis.com

From: Wholley, David (FNIH) [T]
Sent: Wed, 7 Jun 2017 17:50:34 -0400
To: Collins, Francis (NIH/OD) [E]
Subject: FW: Partnership for Accelerating Cancer Therapies
Attachments: PACT Partner Briefing Deck 021017vF4.pdf, PACT Executive Summary 5-3-17.pdf, PACT_Whitepaper_032817.pdf

Hi Francis -- (b) (4), (b) (5)
I have sent Rebecca an update on the other conversations for your meeting Friday. David

From: Collins, Francis (NIH/OD) [E]
Sent: Saturday, May 06, 2017 7:13 AM
To: malles@celgene.com
Cc: Wholley, David (FNIH) [T] <dwholley@fnihi.org>
Subject: Partnership for Accelerating Cancer Therapies

Dear Mark:

It was a pleasure to meet you at the Milken LA meeting, and I'm glad we got a chance to talk about the Partnership for Accelerating Cancer Therapies (PACT), which we have been developing with multiple pharmaceutical companies and FDA over the last eight months or so. As we discussed, PACT is focused on the critical issue of developing better biomarkers for selecting and testing cancer immunotherapies and relevant combinations. Following up your request for more information, I have attached a text executive summary and a slide deck overviewing the partnership, as well as the full text of the white paper that contains the initial research plan for those who may need more detail.

I'm very glad to hear you may be interested in having Celgene consider joining PACT. We are looking to determine a final set of committed partners by the end of June, with the plan to reconvene them thereafter along with our FDA colleagues to work out the final research plan in more detail, so there is still ample room for input here from Celgene should you decide to participate. If you or any of your colleagues want to follow up on the financial implications of participation—or indeed any aspect of PACT—I would ask that you contact David Wholley (copied) at the Foundation for the NIH, who have been overseeing the project development and fundraising aspects of this.

All the best, Francis

Partnership for Accelerating Cancer Therapies (PACT)

Slides for Partner Briefings
February 2017



NIH - 003191

The Foundation for the National Institutes of Health (FNIH) will be the program managers for PACT

The FNIH was established by Congress in 1990 as a not-for-profit 501(c)(3) charitable organization



The Foundation began its work in **1996** to facilitate groundbreaking research at the NIH and worldwide



By creating effective alliances to advance biomedical research



501(c)(3)

Non-governmental
not-for-profit & independent
Board of Directors

More than **550**
projects supported

120+

active research partnerships,
scientific education/training,
conferences/events and
capital programs

93%

of funds directly
support programs



In 2016, Charity Navigator
gave FNIH a 4 star perfect
score rating. The FNIH ranks
in the top 1% of all
organizations ranked

13 years

of outstanding
Charity Navigator ratings

Select partnerships at the FNIH

- | | |
|--|---------------|
| • Accelerating Medicines Partnership NIH (OD), NIA, NIAMS, NIDDK, 10 companies, 9 not-for-profit organizations | \$230 million |
| • Grand Challenges in Global Health (GCGH) Bill & Melinda Gates Foundation | \$201 million |
| • LungMAP: Master Lung Protocol Trial NCI (SWOG), FDA, Friends of Cancer Research, 5 companies to date | \$163 million |
| • Alzheimer's Disease Neuroimaging Initiative (ADNI) NIA, NIBIB, 25+ companies, 3 not-for-profit organizations | \$148 million |
| • Vector-Based Control of Transmission (VCTR) VRC/NIAID, Bill & Melinda Gates Foundation | \$78 million |
| • The Biomarkers Consortium <i>FDA, NIH, CMS, PhRMA, BIO, pharmaceutical and nutrition companies, not-for-profit organizations</i> | \$72 million |
| • Comprehensive T Cell Vaccine Immune Monitoring Consortium (CT-VIMC) Bill & Melinda Gates Foundation, NIAID | \$50 million |
| • MAL-ED: The Interactions of Malnutrition and Enteric Infections, Effect on Childhood Development Bill & Melinda Gates Foundation, Fogarty Institute Center (NIH) | \$46 million |

TOTAL: \$984 million

NIH - 003193

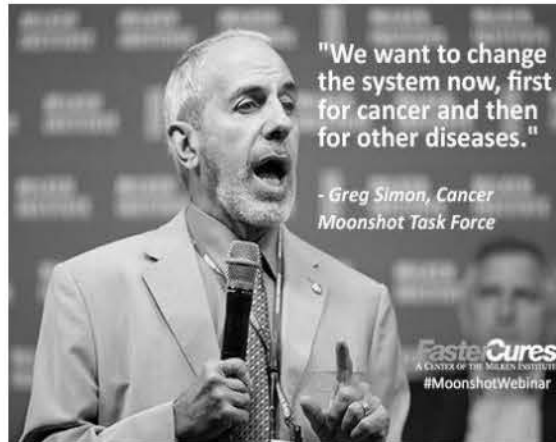
The pursuit of IO and combination therapies faces many challenges

Companies are pursuing hundreds of existing trials, yet:

- + Large number of potential combinations to be tested
 - + Lack of biomarkers to predict and understand patient outcomes
 - + Lack of robust, standardized assays
 - + Lack of reproducibility of data across trials
- = Need to fill knowledge gaps and efficiently use research resources*

Solution: A systematic effort to develop and share biomarker and related clinical data to support clinical testing of combination therapies – PACT

PACT was developed in response to these challenges as one of the Cancer Moonshot Initiative programs



CANCER MOONSHOT



“ I plan to do two things: increase resources—both private and public—to fight cancer, and break down silos and bring all the cancer fighters together—to work together, share information, and end cancer as we know it. ”

Vice President Joseph Biden
February 2016



NIH - 003195

The design of PACT represents consensus from industry, government, and academic experts in the field

PACT is a public-private partnership being developed as part of the Cancer Moonshot effort. FNIH has led an initial research design effort over the past 6 months involving 42 scientists from NCI, FDA, and 14 companies:

- AbbVie
- Amgen
- AstraZeneca
- Bayer
- Boehringer-Ingelheim
- BMS
- EMD Serono
- Genentech
- GSK
- Lilly
- Merck
- Novartis
- Pfizer
- Takeda

- Additional support provided by PhRMA

42 scientists contributed to PACT Design Phase whitepaper

| | | | | |
|---------------------------------------|---|----------------------------|---|-------------------------------|
| <u>INDUSTRY PARTICIPANTS</u> | Axel Hoos (GSK) – Industry Co-Chair | | Jeff Engelman (Novartis) – Industry Co-Chair | |
| | Andrew Schade (Eli Lilly) | David Reese (Amgen) | Greg Plowman (Eli Lilly) | Ute Dugan (BMS) |
| | Jessie English (EMD Serono) | Vicki Goodman (BMS) | Armin Schuler (EMD Serono) | Howard Fingert (Takeda) |
| | Paul Rejto (Pfizer) | Jeff Ecsedy (Takeda) | Bob Abraham (Pfizer) | Stuart Lutzker (Genentech) |
| | Flavio Solca (Boehringer-Ingelheim) | Jianda Yuan (Merck) | Norbert Kraut (Boehringer-Ingelheim) | Thomas J Hudson (AbbVie) |
| | Matthew Albert (Genentech) | Carl Barrett (Astrazeneca) | Chandra Ramanathan (Bayer) | Olaf Christensen (EMD Serono) |
| <u>GOVERNMENT PARTICIPANTS</u> | Helen Chen (NCI-CTEP) – NIH Co-Chair | | Percy Ivy (NCI-CTEP) – NIH Co-Chair | |
| | Magdalena Thurin (NCI) | Tony Kerlavage (NCI) | Lisa McShane (NCI) | Larry Rubinstein (NCI) |
| | Howard Streicher (NCI) | Kevin Howcroft (NCI) | Malcolm Smith (NCI) | Gideon Blumenthal (FDA) |
| | Marc Theoret (FDA) | Reena Phillip (FDA) | Ke Liu (FDA) | Allison Lea (NIH) |
| | Rebecca Baker (NIH) | | | |
| <u>ACADEMIC PARTICIPANTS</u> | Mario Sznol (Yale) | Antoni Ribas (UCLA) | Patricia LoRusso (Yale) | Lillian Siu (PMCC) |
| | Jedd Wolchok (MSKCC) | Steve Hodi (DFCI) | John Byrd (OSU) | Levi Garraway (Broad/Lilly) |
| <u>PACT PROGRAM MANAGEMENT</u> | David Wholley (FNIH) | | | |
| | Stacey Adam (FNIH) | | | |

NIH - 003197

Two PACT program areas emerged from the Design Phase; Program Area 1 will focus on biomarker development and testing and infrastructure creation...

Program Area 1: Facilitate robust, systematic, uniformly conducted clinical testing of known and exploratory biomarkers that enable better understanding of response and resistance to IO combinations and guide treatment strategies

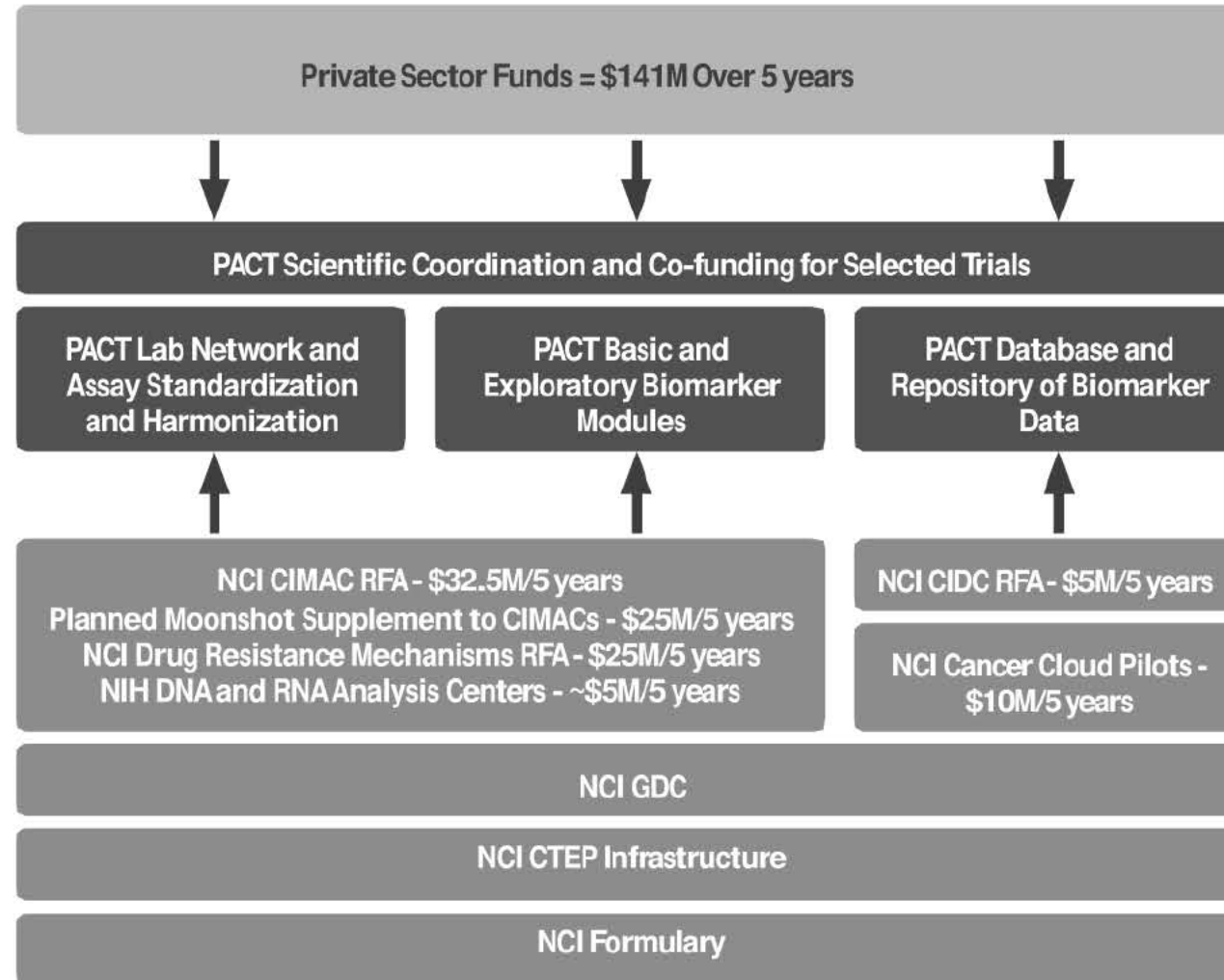
- Establish a **network of 3-5 core laboratories** to conduct, standardize, and validate biomarker assays
- Fund the **development of new exploratory biomarkers and assays** of high relevance to and impact on the field
- **Incorporate biomarker modules into trials** prioritized by PACT and coordinate their adoption broadly across the oncology research community
- Create a **comprehensive database** that integrates biomarker module and clinical data to enable pre-competitive correlative biomarker analyses

...while Program Area 2 will focus on strategic assessment of and outreach to the IO field, as well as coordination and co-funding of selected clinical trials

Program Area 2: Provide scientific coordination for the identification of clinical combination therapy trials important to the field but not already being performed elsewhere, and co-fund such trials with partners.

- Create and maintain a “**landscape analysis**” of combination therapy trials and biomarkers across the IO space, enabling categorization of prospective new trials based on relevance
- Select and **co-fund high relevance combination trials** not already being performed by other entities, leveraging existing trial networks
- **Facilitate information sharing** by all stakeholders to better coordinate clinical/translational oncology programs, **align investigative approaches**, and enable the **most relevant trials to be conducted**
- Includes active outreach to other IO research efforts on an ongoing basis

PACT will build on current and planned NCI investments: recent RFAs and existing infrastructure provide a “shovel ready” foundation for PACT

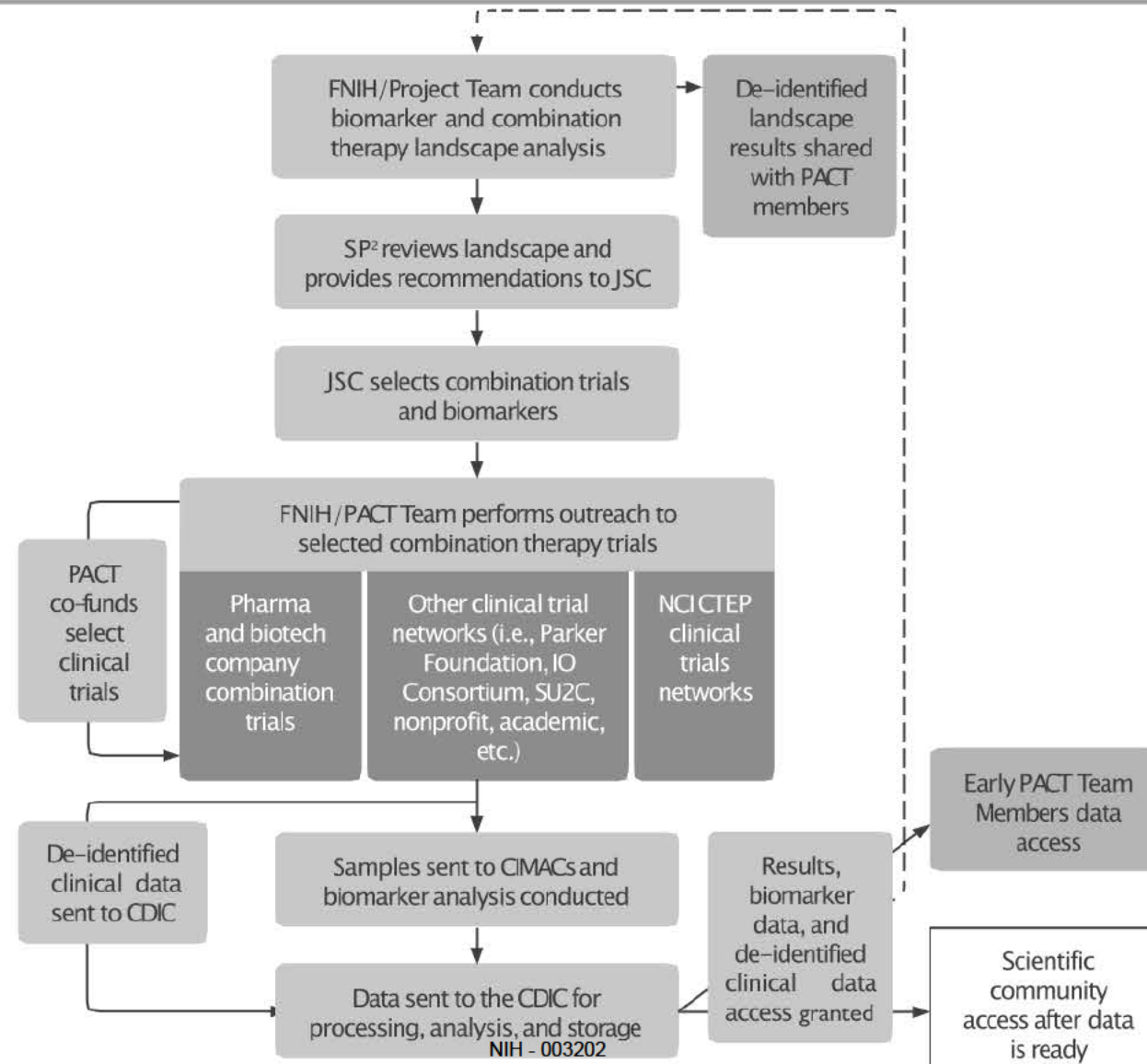


PACT total investment = \$251M over 5 years
NIH - 003200

Three PACT Governance bodies will provide joint oversight – but with streamlined review procedures and policies



PACT offers a flexible, but efficient mechanism to develop novel markers and use them to select and test the most appropriate combination therapies

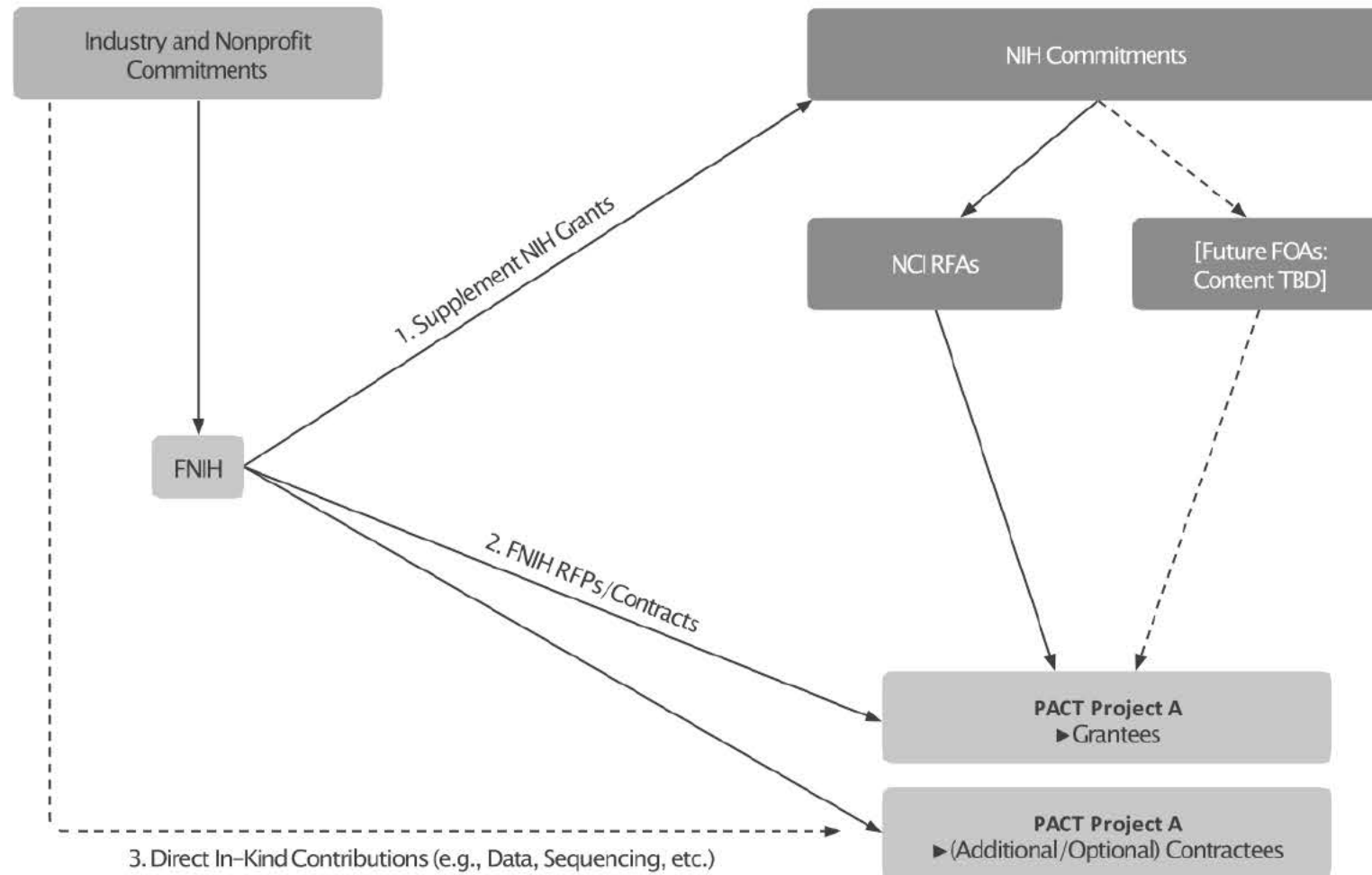


PACT will require total funding of ~\$251M over 5 years, with an investment of ~\$141M/5 years needed from the private sector

| Consolidated Itemized PACT Budget | | |
|---|--|--------------------|
| All Costs Reflect Total Over 5 Years | | |
| Project Plan Section | Budget Item/ Project Goal | Total Project Cost |
| Project 1.1.1 & 1.2 | Create core laboratory network to conduct biomarker assays | (b) (4) |
| Project 1.3 | Create database to bank IO biomarker data from clinical trial | |
| Project 1.4 | Standardize and harmonize biomarker assays for IO therapy | |
| Project 1.1.2 | Development of new IO biomarkers | |
| Project 1.1.2 & 1.4 | Expansion biorepository capabilities for sample storage | |
| Program Area 1 | | |
| Project 2.1 | Conduct bi-annual landscape analysis to determine priority biomarkers and combination therapies Compensate SP ² members for trial and biomarker landscape review | |
| Project 2.2 | PACT co-funding for high priority combination clinical trials | |
| Project 2.3 | Outreach and coordination with other IO efforts | |
| Program Area 2 | | |
| FNIH Program Management Costs | | |
| PACT Initiative Total | | \$251M |
| Program Area 1 –“Buy-up” Option •Supplement to defray costs of tissue collection at clinical sites | | |
| Program Area 2 – “Buy-up” Options •Additional co-funded clinical trials | | |

NIH

Private sector funds for can be deployed flexibly through FNIH to PACT in a variety of ways, as required by specific project needs



NIH - 003204

The collaborative nature of PACT offers distinct—and considerable—value for its stakeholders and the oncology research community at large

- ☑ Core laboratories and database provide access to:
 - Standardized immune biomarkers modules, enabling a systematic approach across trials
 - Standardized, harmonized assay platforms, procedures, and best practices
 - Biomarker analyses to accelerate hypothesis testing
 - Clinical trial and biomarker landscape analyses
- ☑ Opportunities to initiate high relevance trials with PACT co-funding
- ☑ Data and insights to support regulatory decision-making
- ☑ More systematic approach to IO + combinations across the field
- ☑ Mechanism to share insights and resources with other Moonshot and IO collaborations

Private sector funders will have an direct voting role in further defining the PACT research plan and in PACT governing committees

The proposed PACT program also has synergies with several areas of recommendation from the Cancer Moonshot Blue Ribbon Panel

★ Potential PACT synergies

- Network for direct patient engagement
- Cancer immunotherapy translational trials network ★
- Therapeutic target identification to overcome drug resistance ★
- A national cancer data ecosystem for sharing and analysis ★
- Fusion oncoproteins in pediatric cancer
- Symptom management research
- Prevention and early detection: implementation of evidence-based approaches
- Retrospective analysis of biospecimens from patients treated with standard of care ★
- Generation of human tumor atlases ★
- Development of new enabling cancer technologies

Assuming timely success at funding PACT, we are aiming for an operational launch of the initiative in 3Q of this year

Next steps:

- ☐ Finalize PACT budget and white paper, distribute for review (February, 2017)
- ☐ Outreach to potential collaborators (patient organizations, non-profits, other companies, professional and standards organizations, etc.) (February-March, 2017)
- ☐ Partners identified and funds pledged via FNIH (March-June, 2017)
- ☐ FNIH will convene an in-person meeting with committed partners to develop detailed research plans for each project, including detailed budgets, timelines and milestones (3Q, 2017)
- ☐ Desired launch date of PACT (3Q, 2017)

NIH - 003208

Biomarkers to be Included in PACT

BASIC ASSAYS

(To be run on all patients in each trial)

- Peripheral Samples: Flow cytometry and CyTOF – 3 panels - T and B cell
- Tumor: immunohistochemistry
- Peripheral Samples: ELISA
- Whole exome sequencing (150X coverage)
- RNA-seq (150 million reads/sample)
- cfDNA (using DNA-seq)

EXPLORATORY ASSAYS

(Examples)

- Expanded flow cytometry (innate immune cell panels)
- CNVs
- SNPs
- Single cell/nuclei RNA-seq
- CTC
- T and B cell deep receptor sequencing
- cfRNA
- Microbes
- Exosomes
- Microvesicles
- Expanded immunohistochemistry
- Immunofluorescence
- Others TBD

Executive Summary

Recent advances in cancer treatment have offered the prospect of greatly enhanced outcomes, prolonged survival, and cure for some patients. Much of the recent success has been driven by the development of new immuno-oncology (IO) agents, leading to an explosion of translational research as well as investment in the field. To date, however, the improvements in outcomes and cure generated by the monotherapies of these agents are possible only for a minority of patients, and emerging data demonstrate that the greatest impact on cancer treatment will be achieved by combinations of multiple IO agents or of IO and non-IO agents. The successful pursuit of these combination therapies is complicated, however, by the sheer numbers of possible combinations, by high biologic complexity, and by the need for new translational biomarkers and assays to guide which patients should receive which combinations. These challenges are further compounded by the novelty and intensely competitive nature of the IO field, which has encouraged fragmented and at times duplicative research approaches.

To solve these challenges, a systematic cross-sector effort is required to identify and develop robust, standardized biomarkers and related clinical data that support the selection and testing of promising therapeutic combinations. The magnitude of this task and the substantial current knowledge gaps within the field make it unlikely a single stakeholder can execute such a mission alone. As a part of its support of the Cancer Moonshot, the National Institutes of Health (NIH) has proposed a 5-year, ~\$250 million precompetitive public-private research collaboration called the Partnership for Accelerating Cancer Therapies (PACT) to enable achievement of these goals. The initial strategic plan for PACT has been developed through a process led by the Foundation for the NIH (FNIH) with input from 42 key opinion leaders in the cancer field, encompassing representatives from the National Cancer Institute (NCI), U.S. Food and Drug Administration (FDA), academia, and 15 industry partners—AbbVie, Amgen, AstraZeneca, Bayer, Boehringer-Ingelheim, BMS, EMD Serono, Genentech, GSK, Lilly, Merck, Novartis, Pfizer, PhRMA, and Takeda.

PACT aims to accelerate the development of effective combination therapies by enabling critical clinical investigations not covered by others, unifying clinical biomarker investigation, filling knowledge gaps, and integrating information from multiple sources, through two programs:

Program 1: Facilitate robust, systematic, and uniformly conducted clinical testing of basic biomarkers that enable researchers and clinicians to better understand the mechanisms of response and resistance to treatment strategies. PACT will provide a systematic approach to immune and related oncology biomarker investigation in clinical trials by providing standardized biomarker modules, which can be utilized within the PACT programs and across the research community. These modules allow for (a) consistent generation of data, (b) access to uniform and harmonized assays to support data reproducibility, (c) comparability of data across trials, and (d) discovery/validation of new biomarkers for combination immunotherapies and related combinations. Specific elements of the program include the following:

- Providing a set of basic biomarker modules for uniform clinical application.
- Establishing a network of 3–5 core laboratories to coordinate, conduct, validate, and standardize biomarker assays. Funding the development of standardized biomarkers for immunoprofiling and exploratory biomarker assays of high relevance.
- Incorporating biomarkers and data collection standards into trials prioritized through PACT and coordinating their adoption broadly across the IO research community.
- Creating a comprehensive database that integrates biomarker and clinical data to enable pre-competitive correlative biomarker analyses.

Program 2: Provide scientific coordination for the selection of clinical combination therapy trials important to the field but not already being performed elsewhere, and co-fund such trials with partners. This will be accomplished by the following:

- Creating and maintaining a “landscape analysis” of combination therapy trials and biomarkers across the entire IO and oncology space, enabling categorization of prospective new trials based on relevance.
- Selecting and co-funding high relevance combination trials not being performed by other entities, while leveraging significant existing investments (such as in trial networks) made by the government, companies, and nonprofit foundations.
- Facilitating information sharing by all stakeholders to better coordinate clinical/translational oncology programs, align investigative approaches, avoid duplication of effort, share resources, and enable more relevant high-quality trials to be conducted. This will include active outreach to other IO research efforts on an ongoing basis.

The core laboratory, assay development, and database functions required as part of Program 1 will be built on a solid base of research infrastructure and academic grants funded by NCI. Fortunately, NCI has recently released several Requests for Applications (RFAs) in November 2016 that are highly germane to the core goals of PACT (see Appendix 5). Based largely on existing funding from the Precision Oncology Initiative, with additional planned Cancer Moonshot funding, these RFAs seek

applications for ~\$110 million in funding over 5 years beginning in 2017 for a number of Cancer Immune Monitoring and Analysis Centers (CIMACs), a Cancer Immunologic Data Commons (CIDC), and several related initiatives that create integrated multidisciplinary research cores with basic, translational, and computational expertise. Although currently limited as to the number of sites, assays, and data types supported, these grants provide a “shovel ready” foundation for the core lab and database functions required by PACT, particularly when combined with NCI’s recently announced Formulary initiative and its existing national clinical trials network and genomic data management programs.

In addition to supporting these resources, PACT will coordinate and standardize use of existing standardized biomarker assays to most efficiently use available resources. If available, fully validated existing biomarker assays can be conducted through parties outside PACT but channel data into the PACT database, provided assays are performed to PACT standards.

(b) (4)

A joint governance structure will maintain close involvement by all partners in key decisions, consisting of:

- An operationally focused PACT Joint Steering Committee (JSC) to direct the research plan and ensure adherence to project milestones
- A PACT Scientific Project Selection Panel (SP2) to analyze potential therapy/biomarker combinations and advise the JSC regarding fundable PACT studies
- A PACT Executive Committee (EC) to provide strategic direction, communication with partner leadership, and resolution of policy issues.

Voting participation in the JSC and EC will be split 50/50 between government and private sector partners. The SP² will consist of key academic/NCI oncology experts and scientists with industry oncology experience in drug development who lack significant financial and employment ties to individual companies in order to ensure its advisory role is carried out with objectivity and transparency.

All PACT data will be released publicly as promptly and broadly as possible in keeping with NIH’s mission and policy, though also dependent on restrictions in underlying clinical trial and grant agreements. Where feasible, PACT participants will have early access to data, but consistent with these restrictions.

The value proposition for PACT stakeholders, for the oncology field, and for patients will be considerable, providing immediate:

- Access to standardized immune biomarker modules, enabling a systematic and uniform analytical approach across trials
- Access to databases of pre-competitive biomarker analyses, accelerating hypothesis testing and decision-making
- Access to core facilities with standardized analysis platforms, procedures, and best practices, working with regulatory agencies to ensure the highest quality evidence and documentation, relevant to potential registration and labeling
- Access to clinical trial landscape analyses for combination therapies and biomarkers across the entire IO space, and the opportunity to align research priorities, avoid duplication of effort, fill gaps, and share resources
- Opportunities to initiate high relevance trials with company assets for PACT co-funding
- Opportunity to drive new collaborations resulting from PACT insights and contribute to improving cure rates for patients under the goals of the Cancer Moonshot Initiative

(b) (4)

(b) (4) Once key partners are

confirmed, FNIH will reconvene the scientific leads from committed partners to develop a final research plan, including detailed project plans and go/no-go milestones. Given the sense of urgency in addressing patient needs, the timing of NIH funding, and the rapid pace of progress in the field, formal launch of PACT is being targeted for Q3 of 2017.

Partnership for Accelerating Cancer Therapies (PACT)

FINAL DESIGN WHITEPAPER - FEBRUARY 2017



National Institutes
of Health



Foundation for the
National Institutes of Health

PACT Design Phase Sponsors

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National Institutes of Health/National Cancer Institute

U.S. Food and Drug Administration

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Executive Summary

Recent advances in cancer treatment have offered the prospect of greatly enhanced outcomes, prolonged survival, and cure for some patients. Much of the recent success has been driven by the development of new immuno-oncology (IO) agents, leading to an explosion of translational research as well as investment in the field. To date, however, the improvements in outcomes and cure generated by the monotherapies of these agents are possible only for a minority of patients, and emerging data demonstrate that the greatest impact on cancer treatment will be achieved by combinations of multiple IO agents or of IO and non-IO agents. The successful pursuit of these combination therapies is complicated, however, by the sheer numbers of possible combinations, by high biologic complexity, and by the need for new translational biomarkers and assays to guide which patients should receive which combinations. These challenges are further compounded by the novelty and intensely competitive nature of the IO field, which has encouraged fragmented and at times duplicative research approaches.

To solve these challenges, a systematic cross-sector effort is required to identify and develop robust, standardized biomarkers and related clinical data that support the selection and testing of promising therapeutic combinations. The magnitude of this task and the substantial current knowledge gaps within the field make it unlikely a single stakeholder can execute such a mission alone. As a part of its support of the Cancer Moonshot, the National Institutes of Health (NIH) has proposed a 5-year, ~\$251 million precompetitive public-private research collaboration called the Partnership for Accelerating Cancer Therapies (PACT) to enable achievement of these goals. The initial strategic plan for PACT has been developed through a process led by the Foundation for the NIH (FNIH) with input from 42 key opinion leaders in the cancer field, encompassing representatives from the National Cancer Institute (NCI), U.S. Food and Drug Administration (FDA), academia, and 15 industry partners—AbbVie, Amgen, AstraZeneca, Bayer, Boehringer-Ingelheim, BMS, EMD Serono, Genentech, GSK, Lilly, Merck, Novartis, Pfizer, PhRMA, and Takeda.

PACT aims to accelerate the development of effective combination therapies by enabling critical clinical investigations not covered by others, unifying clinical biomarker investigation, filling knowledge gaps, and integrating information from multiple sources, through two programs:

Program 1: Facilitate robust, systematic, and uniformly conducted clinical testing of basic biomarkers that enable researchers and clinicians to better understand the mechanisms of response and resistance to treatment strategies. PACT will provide a systematic approach to immune and related oncology biomarker investigation in clinical trials by providing standardized biomarker modules, which can be utilized within the PACT programs and across the research community. These modules allow for (a) consistent generation of data, (b) access to uniform and harmonized assays to support data reproducibility, (c) comparability of data across trials, and (d) discovery/validation of new biomarkers for combination immunotherapies and related combinations. Specific elements of the program include the following:

- ▶ Providing a set of basic biomarker modules for uniform clinical application.
- ▶ Establishing a network of 3–5 core laboratories to coordinate, conduct, validate, and standardize biomarker assays.

- ▶ Funding the development of standardized biomarkers for immunoprofiling and exploratory biomarker assays of high relevance.
- ▶ Incorporating biomarkers and data collection standards into trials prioritized through PACT and coordinating their adoption broadly across the IO research community.
- ▶ Creating a comprehensive database that integrates biomarker and clinical data to enable pre-competitive correlative biomarker analyses.

Program 2: Provide scientific coordination for the selection of clinical combination therapy trials important to the field but not already being performed elsewhere, and co-fund such trials with partners. This will be accomplished by the following:

- ▶ Creating and maintaining a “landscape analysis” of combination therapy trials and biomarkers across the entire IO and oncology space, enabling categorization of prospective new trials based on relevance.
- ▶ Selecting and co-funding high relevance combination trials not being performed by other entities, while leveraging significant existing investments (such as in trial networks) made by the government, companies, and nonprofit foundations.
- ▶ Facilitating information sharing by all stakeholders to better coordinate clinical/translational oncology programs, align investigative approaches, avoid duplication of effort, share resources, and enable more relevant high-quality trials to be conducted. This will include active outreach to other IO research efforts on an ongoing basis.

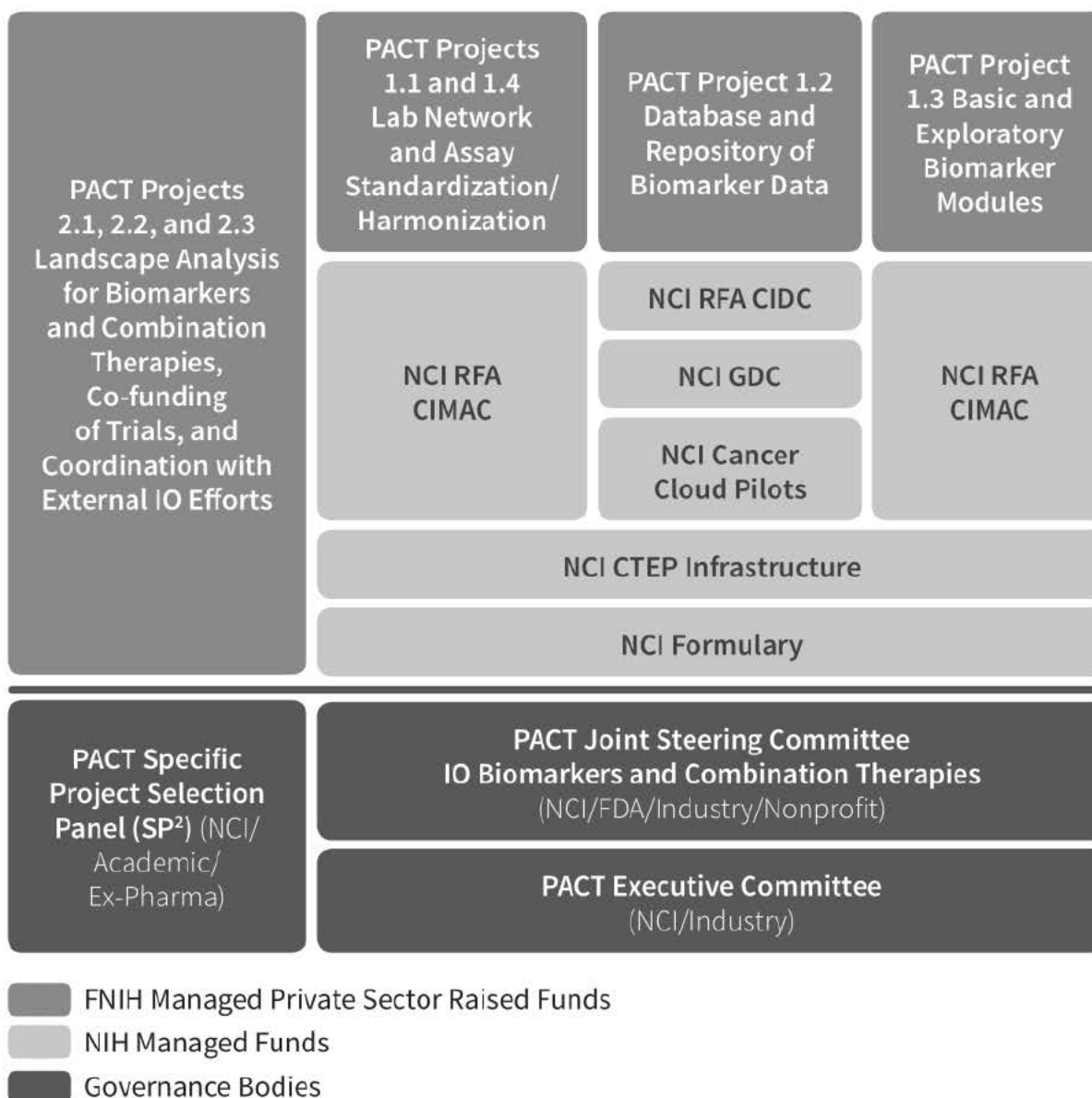
The core laboratory, assay development, and database functions required as part of Program 1 will be built on a solid base of research infrastructure and academic grants funded by NCI. Fortuitously, NCI has recently released several Requests for Applications (RFAs) in November 2016 that are highly germane to the core goals of PACT (see **Appendix 5**). Based largely on existing funding from the Precision Oncology Initiative, with additional planned Cancer Moonshot funding, these RFAs seek applications for ~\$110 million in funding over 5 years beginning in 2017 for a number of Cancer Immune Monitoring and Analysis Centers (CIMACs), a Cancer Immunologic Data Commons (CIDC), and several related initiatives that create integrated multidisciplinary research cores with basic, translational, and computational expertise. Although currently limited as to the number of sites, assays, and data types supported, these grants provide a “shovel ready” foundation for the core lab and database functions required by PACT, particularly when combined with NCI’s recently announced Formulary initiative and its existing national clinical trials network and genomic data management programs.

In addition to supporting these resources, PACT will coordinate and standardize use of existing standardized biomarker assays to most efficiently use available resources. If available, fully validated existing biomarker assays can be conducted through parties outside PACT but channel data into the PACT database, provided assays are performed to PACT standards.

The additional ~\$141 million/5 years required to meet the baseline PACT goals will be raised through FNIH. A majority of these funds will be used to supplement NCI grants, although funds may be disbursed directly through FNIH contracts where appropriate. Additional funds may be sought later for future projects of interest to further PACT partnerships and goals.

A joint governance structure will maintain close involvement by all partners in key decisions, consisting of:

- ▶ An operationally focused PACT Joint Steering Committee (JSC) to direct the research plan and ensure adherence to project milestones
- ▶ A PACT Scientific Project Selection Panel (SP²) to analyze potential therapy/biomarker combinations and advise the JSC regarding fundable PACT studies
- ▶ A PACT Executive Committee (EC) to provide strategic direction, communication with partner leadership, and resolution of policy issues.



Voting participation in the JSC and EC will be split 50/50 between government and private sector partners. The SP² will consist of key academic/NCI oncology experts and scientists with industry oncology experience in drug development who lack significant financial and employment ties to individual companies in order to ensure its advisory role is carried out with objectivity and transparency.

All PACT data will be released publicly as promptly and broadly as possible in keeping with NIH's mission and policy, though also dependent on restrictions in underlying clinical trial and grant agreements. Where feasible, PACT participants will have early access to data; however, data will be retained for analysis and not released publically until study analysis is complete and closed to accrual and treatment in concert with our research agreements for a reasonable time.

The **value proposition** for PACT stakeholders, for the oncology field, and for patients will be considerable, providing immediate:

- ▶ Access to standardized immune biomarker modules, enabling a systematic and uniform analytical approach across trials
- ▶ Access to databases of pre-competitive biomarker analyses, accelerating hypothesis testing and decision-making
- ▶ Access to core facilities with standardized analysis platforms, procedures, and best practices, working with regulatory agencies to ensure the highest quality evidence and documentation, relevant to potential registration and labeling
- ▶ Access to clinical trial landscape analyses for combination therapies and biomarkers across the entire IO space, and the opportunity to align research priorities, avoid duplication of effort, fill gaps, and share resources
- ▶ Opportunities to initiate high relevance trials with company assets for PACT co-funding
- ▶ Opportunity to drive new collaborations resulting from PACT insights and contribute to improving cure rates for patients under the goals of the Cancer Moonshot Initiative

(b) (4)

Introduction

Over the last decade, cancer treatment options have substantially improved, now offering the prospect of greatly enhanced outcomes prolonged survival or cure for some patients. To date, such outcomes are only possible for a minority of patients; however, there is significant potential to expand this benefit to a broad majority of patients in many cancers.

Recently, the positive clinical outcomes associated with progress in cancer treatments have largely been driven by IO agents, which stimulate the immune system to eradicate or control cancer cells. The success of IO therapies in the treatment of melanoma, renal cell carcinoma, NSCLC, as well as some rare tumors such as Merkel cell tumors and Hodgkin's lymphoma has led to a rapid explosion of investments in IO research by the pharmaceutical industry, academic institutions, government, and nonprofit organizations. IO's greatest impact on cancer treatment is expected from combination therapies involving both multiple IO and complementary non-IO agents and will require systematic investigation of a large spectrum of new agents across the portfolio boundaries of individual companies. Despite the great resources invested in IO and related combination regimens to date, the task is complicated by high biologic complexity, the need for translational biomarkers to direct therapy, and the deeply competitive nature of the field, which has led to some redundant research and development efforts, duplication of costs and resources, and the absence of systematic approaches to scientific investigation.

To achieve the desired improvement in outcomes for a majority of patients, a systematic effort across a complex spectrum of pharmaceutical, biotech, academic, government and nonprofit stakeholders is required to effectively test therapeutic combination options and identify biologic markers that direct the right treatment combination to the right patient. This idea has long been gaining followers in the IO field and potential methods for addressing it have been laid out by key scientists in the field (Hoos, Britten, Huber, & O'Donnell-Tormey, 2011). However, the magnitude of this task and the substantial knowledge gaps that still exist make it unlikely that any single stakeholder can execute the task alone. A public-private research partnership such as PACT offers a unique opportunity to address this challenge by coordinating resources across NIH, FDA, biopharmaceutical companies, and patient groups using a focused, collaborative approach. PACT aims to accelerate progress toward improved outcomes by facilitating and enabling critical investigations not covered by others, thus filling knowledge gaps and integrating information from multiple sources across the cancer research sphere.

PACT will establish two program areas that will help determine high priority combination therapies and biomarkers (to be tested by PACT and others in the IO field) and generate the knowledge needed to reduce the number of unnecessary combination trials and improve patient participation in such trials.

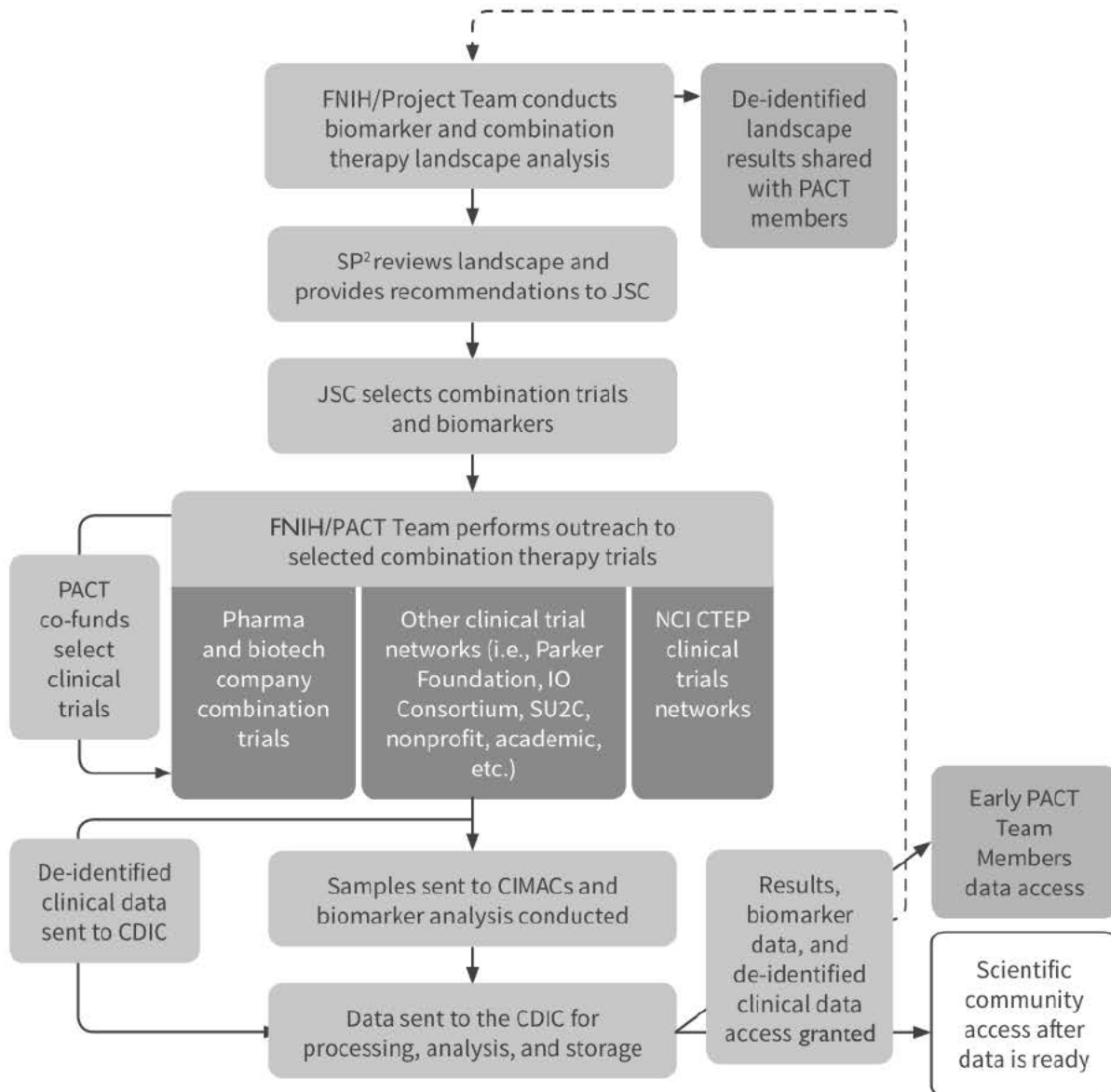
Program Area 1 will facilitate robust, systematic, and uniformly conducted clinical testing of basic biomarkers that enable researchers and clinicians to better understand the mechanisms of response and resistance to treatment strategies. PACT will provide a systematic approach to

immune and related oncology biomarker investigation in clinical trials by providing standardized biomarker modules, which can be utilized within the PACT programs and across the research community. These modules allow for (a) consistent generation of data, (b) access to uniform and harmonized assays to support data reproducibility, (c) comparability of data across trials, and (d) discovery/validation of new biomarkers for combination immunotherapies and related combinations. Specific elements of the program include the following:

- ▶ Providing standardized biomarker modules for uniform clinical application across the community.
- ▶ Establishing a network of 3–5 core laboratories to coordinate, conduct, validate, and standardize biomarker assays and data collection standards.
- ▶ Funding the development of standardized biomarkers for immunoprofiling and exploratory biomarker assays of high relevance.
- ▶ Incorporating biomarkers into trials prioritized through PACT and coordinating their adoption broadly across the IO research community.
- ▶ Creating a comprehensive database that integrates biomarker and clinical data to enable pre-competitive correlative biomarker analyses.

Program Area 2 will provide scientific coordination for the selection of clinical combination therapy trials important to oncology but not already being performed elsewhere, and co-fund a carefully selected subset of such trials with partners. This will be accomplished by the following:

- ▶ Creating and maintaining a “landscape analysis” of combination therapy trials and biomarkers across the entire IO space, enabling categorization of prospective new trials based on relevance.
- ▶ Selecting and co-funding high relevance combination trials not being performed by other entities, while leveraging significant existing investments (such as trial networks) made by the government, companies, and nonprofit foundations.
- ▶ Facilitating information sharing by all stakeholders to better coordinate clinical/translational oncology programs, align investigative approaches, avoid duplication of effort, share resources, and enable more relevant high-quality trials to be conducted. This will include active outreach to other IO research efforts on an ongoing basis.



Value Proposition

The value proposition for participating stakeholders in PACT will be considerable:

- ▶ Access to an infrastructure for incorporating standardized immune biomarker modules in clinical trials, enabling a systematic analysis approach across trials, with reproducible assay results, reduced costs and resources, and enhanced power of correlative analysis
- ▶ Access to core facilities with standardized analysis platforms, procedures, and best practices, working with regulatory agencies to ensure the highest quality evidence and documentation, also relevant to potential registration and labeling
- ▶ Access to a comprehensive database for pre-competitive correlative biomarker analyses, accelerating data acquisition and hypothesis testing, and enhancing decision-making
- ▶ Enhanced reliability and speed of clinically relevant biomarker identification for identifying patients who will benefit from specific immunotherapy agents or combinations
- ▶ Opportunity to be the first to initiate a high relevance trial with the company's asset of interest, co-funded by PACT or its partners (e.g. NCI)
- ▶ Access to and participation in the coordination of clinical and translational programs across organizations in the IO space (pharmaceutical companies, biotech, academia, government, and nonprofits) to align investigative approaches, avoid duplication of effort, share/preserve resources, and thus allow for more relevant trials to be conducted
- ▶ Access to and participation in the creation of an up-to-date clinical trial landscape analysis for combination therapies across the entire IO space, including access to information about relevant investigations not yet covered by any party.
- ▶ Contributing to the goal of the U.S. Cancer Moonshot Initiative of doubling the rate of progress in cancer research and delivering more cures to patients
- ▶ Opportunity to drive new collaborations resulting from the insights of the PACT partnership

Program Area 1: Facilitate robust, systematic, and uniformly conducted clinical testing of basic biomarkers that enable researchers and clinicians to better understand the mechanisms of response and resistance to treatment strategies

Objective

To reach the next level of benefit of immunotherapy for a broader number of patients, it is necessary to understand and characterize the complexity and dynamics of the immune state in cancer patients and the therapeutically induced changes in immune profiles in the tumor and the periphery.

Experimental findings point to the value of biomarkers for cancer immunotherapy in predicting benefit of therapy and understanding the mechanisms of resistance. For example, high tumor expression of PD-L1 is predictive of increased likelihood of clinical benefit from anti-PD-1 monotherapy in patients with NSCLC. Other factors associated with response include high mutational load, inflammatory gene signatures, and tumor-infiltrating lymphocytes. More recently, tumor genomic studies in patients treated with checkpoint inhibitors have revealed mutations in interferon response pathway genes as a potential mechanism of primary or acquired resistance. While these results are promising, systematic testing in larger patient cohorts is needed to confirm preliminary analyses and clinically validate predictive biomarker candidates.

PACT will provide the foundation for harmonizing the use of biomarker assays, data collection, and data banking, as well as optimize systematic biomarker incorporation into clinical trials to understand response and resistance to cancer immunotherapies and to enable new treatment strategies. Specifically, projects under Program Area 1 will address a few key challenges: inconsistent analytical validation standards and assay methodologies across trials, limited power of individual trials, and lack of common data platforms for combined analysis and cross validation across trials. Project 1.1 lays out the biomarkers the PACT team proposes to systematically incorporate into clinical trials as standard practice, while Projects 1.2, 1.3, and 1.4 detail the infrastructure that will be established to evaluate these proposed biomarkers in clinical trials.

Project 1.1—Establishing biomarker modules for systematic and uniform biomarker testing in clinical trials (for PACT and non-PACT studies)

Challenge/Opportunity

The lack of validated biomarkers and the current inability to compare data between clinical trials is a major challenge and partly driven by the absence of uniform and systematic biomarker investigation. This also limits the selection of the most appropriate immunotherapy regimen (single agent or combination therapy) for a given cancer patient based on validated markers. The fundamental lack of understanding of mechanistic interplay between the tumor and human immune system is a major hurdle for patient selection in IO/oncology clinical trials. Lack of data sets that encompass the molecular characterization of the tumor microenvironment (TME) correlated with clinical outcomes needs to be evaluated in appropriately sized patient data sets with a well-defined statistical analysis plan. Moreover, pharmacodynamic biomarkers can provide an early understanding about performance of a new agent or new combination, accelerating decision-making and prioritization. Comparable data sets from most trials conducted by stakeholders in the community, which close data gaps and allow for more systematic analyses, are needed to build validated biomarkers and truly effective patient selection strategies.

Solution

The PACT initiative will select biomarkers that are relevant to the testing of IO agents in clinical trials and that will help researchers to understand key biologic processes and to optimize decision-making in the application of existing and novel therapeutics. Biomarkers will be grouped in “modules”, a set of studies or analyses built around specific biological topics or areas of inquiry (for example, immune cell biology or liquid biopsies). Modules will fall into two categories: basic and exploratory.

Basic modules address commonly used or known biomarkers which can be reliably tested by a broad spectrum of clinical trials. They are fundamental to investigating specific aspects of cancer biology and building baseline data for how immunotherapy treatments effect this biology, have current clinical utility, and should be executable by the majority of trial sponsors in the oncology field. Basic modules must to be usable by a majority of investigators. They are meant to be broadly applicable to most trials and still deliver insights for specific trials.

Exploratory modules will test novel or less well-established markers), and represent an expansion into new areas of science or technology which need further validation or which PACT participants may not be positioned to (or not desire to) study on their own. They are meant to address a specific biology question of interest relevant to each specific trial. Exploratory modules can be added to PACT on an optional basis until enough evidence consistently demonstrates their relevance and applicability so that they can be considered basic standard biomarkers. The exploratory biomarker modules will accommodate new scientific and biomarker discoveries and advances to be introduced and tested by a few investigators initially. Exploratory biomarkers

can cover all types of new assays being developed for tracking treatment response, including imaging, sequencing, proteomics, immunohistochemistry (IHC) multiplexing, and single-cell analysis.

Modules are expected to be used as follows:

1. All PACT-associated studies will be required to test PACT basic biomarker modules—i.e., meaning each study participating in PACT will need to run the basic modules.
2. NCI will adopt PACT biomarker module recommendations for all NCI studies whenever feasible. These efforts will be synergized with the assays being selected for the CIMAC laboratory network.
3. PACT partners and collaborators will be asked to use PACT selected biomarkers with the aim to standardize and harmonize data generation and collection in studies outside of PACT. The use of these biomarkers can either be through the use of the CIMACs or through use of standardized protocols. The process of selecting these non-PACT, external trials to use the CIMACs will be facilitated through the Scientific Project Selection Panel (SP²) and the Joint Steering Committee (JSC).

Each basic biomarker module will employ comparable methods across all participating medical centers and trials. Such comparability will require selection of assays with similar specifications and harmonization of the assays used across participating centers. If achieved, this will allow the cross comparison and coordinated analysis of data across multiple trials.

In addition, the PACT initiative will need to identify clinical trials from which standard biomarkers and/or samples can be collected that can be used to characterize or validate novel Exploratory biomarkers. PACT will place emphasis on identifying combination therapy clinical trials where collecting biomarker information is a high priority to the IO community. The understanding of the mechanisms of response and resistance to IO therapies that will result from the biomarker analyses will aid in the further refinement and selection of combination therapies for future testing.

PACT will not establish its own clinical trials network infrastructure or fully sponsor trials itself, but will partner with and utilize existing clinical trials networks, such as the NCI's National Clinical Trials Network (NCTN) and Experimental Therapeutics Clinical Trials Network (ETCTN), or networks established by nonprofit organizations or industry sponsors. The SP² will identify these trials based on the periodic landscape analyses that will be conducted as part of PACT and pass their recommendations to the JSC. The JSC and the PACT outreach team can work with these external networks or sponsors to help broker a partnership with PACT on those trials resulting in eventual deposition of the relevant biomarker and clinical data into the common PACT database. PACT will also consider providing supplementary funding to conduct these trials in selected cases. This process for trial selection is further described below in **Program Area 2**.

Focus of the Project

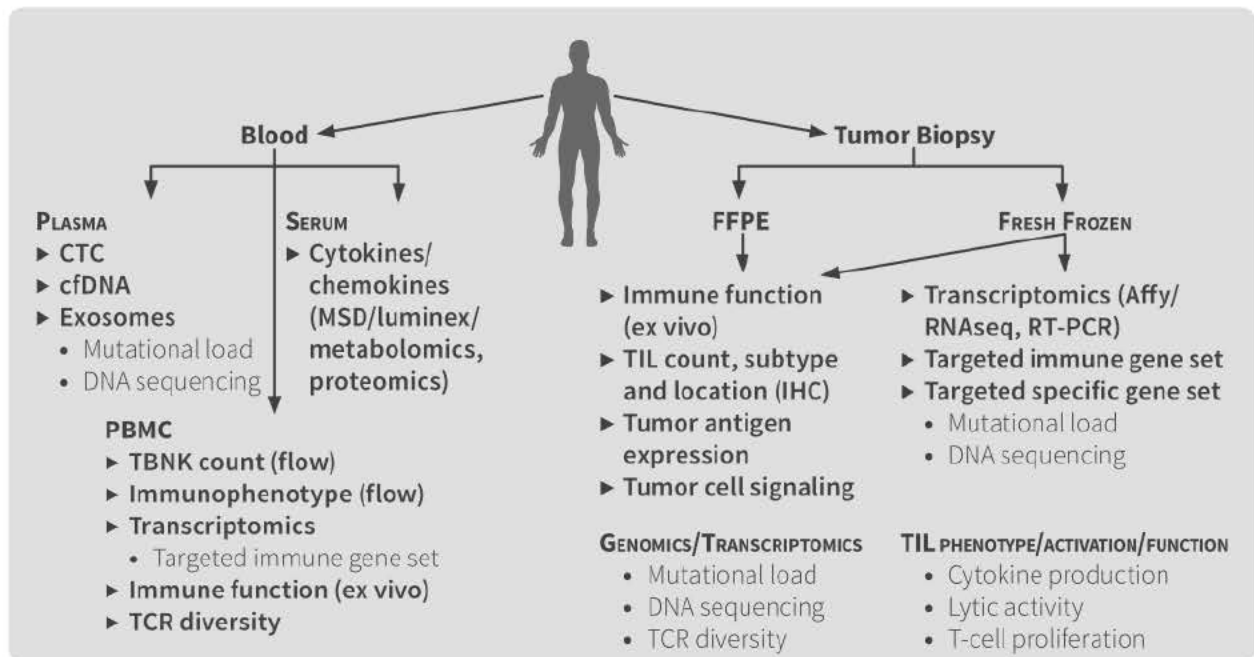
As described above, two types of biomarker “modules” will be pursued for PACT: basic and exploratory modules. Table 1 describes the modules defined thus far by the PACT Working Groups. This table is divided by basic and exploratory modules and defines what tissue collection will be necessary for each.

| TABLE 1. PROPOSED PACT BIOMARKER MODULES | | | |
|--|---|---|--|
| MODULE # | BIOLOGY TO BE STUDIED | DESIRED ASSAYS | SAMPLE REQUIREMENT |
| BASIC | | | |
| 1A | Immune cell biology | Periphery: Flow cytometry and CyTOF—3 (T and B cell panels) Tumor: IHC | Blood, tumor biopsies (core and bulk) |
| 1B | Peripheral cytokines/chemokines | ELISA | Blood/serum |
| 2A | Cancer genetics / somatic mutations | Whole exome sequencing (100X coverage—per standard practice) | Tumor biopsies (core and bulk), blood— isolated DNA 200-500 ng |
| 3A | Transcriptomics of the tumor microenvironment | RNA-seq (150 million reads/sample) | Tumor biopsies (core and bulk), blood |
| 4A | Liquid biopsy | cfDNA assay | Blood— Streck or EDTA tube |
| EXPLORATORY | | | |
| 1c | Immune cell biology | Expanded flow cytometry (innate immune cell panels) | Tumor biopsies (core and bulk), blood |
| 2B | Cancer genetics / somatic mutations | CNVs, SNPs, T and B cell deep receptor sequencing | Tumor biopsies (core and bulk), blood |
| 3B | Transcriptomics of the tumor microenvironment | Single cell/nuclei RNA seq, others TBD | Tumor biopsies—single cell isolates, blood |
| 4B | Liquid biopsy | CTC, cfRNA, exosomes, microvesicles, others | Blood—collection tubes TBD |
| 5 | Defining the microbiome | Microbes and others (see section below) | Stool, saliva, others TBD |
| 6 | Non-immune tumor architecture | IHC, IF, others TBD | Tumor biopsies (core and bulk) |

Basic biomarkers will be standard and mandatory for all PACT biomarker analyses, subject to the sample collection limitations for each trial; exploratory biomarkers will be optional. Biomarkers selected for the basic modules will be harmonized with the assays and platforms named in the CIMAC RFAs. The PACT team has established the priority ranking for mandatory modules: 1a > 2a > 4a > 3a > 1b. Exploratory modules can be conducted at the discretion of PIs; however, if these modules are run, the data generated should be captured in the PACT database. The consistent acquisition of such data across all PACT-related studies will constitute a major advance.

Common Tissue Collection Needs for Biomarker Modules

Any biomarker investigation is only as good as the quality of human samples collected and the reproducibility of the assays used. PACT intends to address both of these issues through careful collection and standardization of biomarker assays. An initial schema for biomarker testing has been outlined as follows:



Baseline Tumor, During Treatment, and Post Treatment (When Possible):

- ▶ Bulk tumor resection (fresh)
- ▶ Core biopsy materials
- ▶ Blood
 - ▷ Standardized whole blood and plasma collection (optional banking protocol)
 - ▷ EDTA tubes, Red top serum tubes, CPT tubes with sodium heparin, and others
- ▶ Bone marrow for hematologic malignancies

- ▶ Standard tissue processing procedures
 - ▷ FFPE
 - ▷ Snap frozen—referred for DNA extraction
 - ▷ RNAlater
 - ▷ Single cell suspension
 - Tissue process with or without enzyme digestion
 - Cell freezing media and standard operation procedure
- ▶ Standard operating procedures (SOP) for dual extraction of DNA and RNA if possible should be explored
 - ▷ Isolated DNA necessary for samples for WES—200–500 ng
- ▶ Emerging tissue processing approaches
 - ▷ Single nuclei recovery for RNA-seq
 - ▷ Smart Tube system for flow cytometry (<http://smarttubeinc.com/index.htm>)
- ▶ Potential biomaterials for microbiome sampling
 - ▷ Serum
 - ▷ Mucosal (Oral swabs, endoscope)
 - ▷ Urine/Fecal
 - ▷ Tumor

Tissue Collection

It is anticipated that tissue collection including blood draws, biopsies and other specimen collections could cost up to \$5,000/patient/time point, if specimen processing is included in the estimated costs. The PACT team anticipates this cost will likely be covered by the groups sponsoring the trials, and that PACT would support the actual conduct of the biomarker assays in the CIMAC laboratories. As a potential optional incentive for trials to participate in PACT, the PACT team could choose to subsidize this cost for trial sites; however, this would need to be a buy-up option, and PACT would likely not be able to support the full \$5,000. This is therefore listed in the budget as a buy-up option at \$7.5 million over 5 years.

Establishing a Biospecimen Repository

Establishing a biospecimen repository will be necessary to allow for easier centralized storage, processing, and accessioning of samples for those trials where further biomarker assays maybe required or desired in the future. This will be especially critical for PBMCs, cfDNA, and other liquid biopsy assays, where a given trial may want to store samples for batch runs or for development of future assays and technologies. Two clear models for biobanking could be established:

- 1) decentralized sample collection, with centralized storage, and centralized database/informatics and
- 2) decentralized sample collection, with decentralized storage, and centralized

informatics. PACT proposes to follow the second model, since PACT trials will be run by multiple organizations, and there will likely be a need to allow the industry trials to retain possession of samples from the trials that they exclusively fund but use PACT biomarker modules or PACT core laboratories. However, PACT will, where possible, recommend that centralized storage also take place.

One option for utilizing existing infrastructure for centralized storage would be to use existing biospecimen repositories at NCI. Both the NCTN and the ETCTN already have biorepositories, and private funding could be used to supplement the grants that already sponsor these repositories. Regardless of where the specimens are stored, the PACT effort will require a centralized accessioning of the samples for initial processing before being sent to the CIMACs for processing. This will allow for accurate tracking of all biospecimens that are part of the PACT effort and could potentially be used for future testing.

Biospecimen Repository Expansion Budget

Supplementing the existing biospecimen repositories at NCI will likely cost ~\$1 million to \$2 million per year to process, accession, and store the samples for the potential 720+ patient samples that are currently due to be collected as part of the CIMACs or external trials. This number would increase if the number of patients were to scale up. This means that a total of as much as \$10 million over 5 years would be necessary for this effort. If PACT were to establish an independently run biorepository, the cost would likely be much greater than this amount. Therefore, \$10 million dollars over 5 years has been added to the PACT budget estimate (see the table at the end of this section.)

1.1.1—Basic Modules

The PACT team had proposed that IHC/flow cytometry (depending on tumor type) and DNA sequencing should be the top priority modules. RNA-seq should be a second priority, unless a particular study mandates a need for this assay. These core modules were selected by the PACT team because they provide a solid knowledge base for cross-comparison of clinical trials that are testing IO therapies. In addition, these modules are well developed and offer good options for standardized assay platforms, as well as analysis techniques. However, a common platform for each module will still need to be selected as part of the research plan for this project for PACT. Platforms and analysis techniques will be selected by the JSC in consultation with the CIMAC team.

Focus of the Project

Mandatory biomarkers will be prioritized by tissue availability and trial needs, but the mandatory modules run for PACT will be standardized across all trials. This means that for some trials not all modules will be used, so PACT has ranked the assays based on amounts of tissue (see above).

Biomarker Module 1: Immune Biology

Focus of the Project

Module 1 is organized into two categories of focus: peripheral samples (i.e., circulating soluble or cell-based biomarkers) and tumor samples. Samples of peripheral blood and resection or biopsy of tumor tissue will be collected, and broad testing is planned.

Module 1a: Immune Cell Biology

Peripheral Specimens

Peripheral samples of blood, serum, or plasma should be collected at multiple time points throughout the course of treatment to allow for longitudinal evaluation of changes in immune biology and, if possible, to correspond with measures of drug exposure. These time points and sample sizes will be dictated by individual clinical protocols. Assays for characterizing the functionality of immune cells by in vitro stimulation can also be developed and will constitute the third flow cytometry panel for Module 1a basic biomarkers.

To analyze peripheral samples, the most common technologies used are flow cytometry and CyTOF for cell based analyses and ELISA-based methodologies for measurement of soluble markers. For a basic evaluation of immune cell biology in the periphery, the panels listed below in Table 2 are recommended. In addition, markers of functional characterization of isolated PBMCs are shown.

TABLE 2. T CELL MARKER PANELS BY FLOW CYTOMETRY

| ACTIVATION | EXHAUSTION | FUNCTIONAL |
|--------------|--------------|--------------|
| LIVE OR DEAD | LIVE OR DEAD | LIVE OR DEAD |
| CD3 | CD3 | CD3 |
| CD4 | CD4 | CD4 |
| CD8 | CD8 | CD8 |
| CD45RO | CD45RO | IFN γ |
| CD69 | LAG3 | TNF α |
| ICOS | TIM3 | GZMB |
| OX40 | CD161 | IL-2 |
| FOXP3 | | |
| CD127 | | |

In Vitro Functional Characterization of PBMCs

- Ag recall
- Epitope spreading
- MLRs

Tumor

Obtaining multiple samples of tumor tissue must be attempted throughout the course of a patient's treatment to allow for longitudinal evaluation of immune response depending upon the needs of the protocol.

Tissues will be collected by resection and/or biopsy. These samples can be fixed, frozen, or used immediately for IHC, gene expression, and TIL analyses (by flow cytometry). Similarly, TILs, once isolated and if sufficient, can be used for in vitro stimulations for cytokine analyses. Specific protocols for sample collection and assay execution are to be defined. For the IHC-based assays, standardized quantitative imaging analysis methodologies will be developed. For flow cytometry-based assays, standardized methods for cell gating will be employed. Tissue is less readily available at multiple sampling points and will be prioritized for use in testing for biomarkers. Evaluation by multiplex IHC will take precedence over flow cytometry and in vitro analyses of immune function, as the recovery of isolated TILs from biopsies may not be sufficient. An example basic panel for IHC is shown in Table 3.

TABLE 3. MARKERS (IHC)

| | | |
|--------|------|-------|
| CD3 | CD16 | PD1 |
| CD8 | CD56 | MHC-1 |
| CD45RO | CD19 | TIM3 |
| CD4 | CD68 | LAG3 |
| FOXP3 | | |

Value Proposition

Data from this module will add to the overall information to understand mechanisms of action for the intervention, mechanisms of therapeutic sensitivity and resistance, and patient selection leading to efficacy.

Approximate Module Budget

Periphery: This estimate is based on a six panel flow analysis, including a measure of receptor occupancy, which should be ~\$2,500–\$3,000/sample. However, this cost may be reduced if we are able to use bulk rates and synergized cost structures within the CIMACs network.

Tumor: This estimate is based on using a simple or single biomarker IHC approach. It should be noted that this approach uses the most tissue.

The cost for this analysis will be ~\$250–\$300/marker. The total cost for the panel is approximately \$3,250–\$3,900/sample. An alternative approach will be to generate multicolor IHC panels that will lead to less utilization of tumor tissue and may provide a moderate cost improvement.

Module 1b: Cytokines/Chemokines Periphery

Multiplex cytokine evaluations using one of the several ELISA-based platforms, such as Mesoscale, ELISA, or Luminex, will be used to test several circulating cytokines in the plasma/serum. The markers will include mediators of immune activation, inflammation, target cell killing, and safety signals such as those of the cytokine release syndrome shown in Table 4.

TABLE 4. SOLUBLE FACTORS

| | | |
|--------------|--------------|----------------|
| G-CSF | IL17 | GZMA |
| GM-SCF | IL2 | GZMB |
| IFN γ | IL4 | PERFORIN |
| IL1 | IL6 | CCL2 |
| IL10 | CXCL2 | CCL3 |
| IL12 | IL7 | CCL8 |
| IL13 | M-CSF | CCL5 |
| IL15 | TGF β | CX3CL1 |
| IL16 | TNF α | CXCL10 (IP-10) |
| IL21 | | CXCL9 (MIG) |

Multiplex Immunoassays**► Immune activation**

- Cytokines
- Chemokines
- Inflammatory mediators

► Safety

- CRS-targeted panel

Approximate Module Budget

This estimate is based on a 29-panel multiplex ELISA-based platform which will be ~\$500–\$600/sample, depending on the choice of platform.

Module 2a: Cancer Genetics/Somatic Mutations

Advances in genome sequencing technologies at affordable cost along with progress in bioinformatics has propelled the field of somatic cancer genetics into a new era. The exponential growth of cancer genome datasets has been justified as a means to identify new cancer genes and pathways that could be the basis for molecular classification of tumors, initiate novel target-based drug discovery programs, and perform molecular profiling of tumors to match therapies with patient-specific genetic alterations. The relevance of mutated antigens in the field of tumor immunology (Gilboa, 1999) has been corroborated by studies of patients receiving checkpoint inhibitors that reported significant clinical benefits correlating with mutational and neoantigen loads (Miao & Van Allen, 2016; Rizvi et al., 2015; Snyder et al., 2014). In addition, tumors with a large number of somatic mutations due to mismatch-repair defects have been shown to be susceptible to immune checkpoint PD-1 blockade therapy (Le et al., 2015). The basis for this correlation is that an increased number of mutations will increase the number of neoantigen specific T-cells capable of eliciting a strong immunogenic response; the very checkpoint blockade that impedes the tumor's ability to suppress neighboring T-cells results in an increase in tumor-cell killing in the presence of a highly immunogenic tumor.

Focus of the Project

To continue to expand on this somatic mutation knowledge and assure that it can be leveraged to determine novel genetic biomarkers related to immunotherapy, the PACT team proposed to conduct whole exome sequencing (WES), taking into account the following principles.

Matched normal tissue: In order to ascertain whether a sequence variant found in a tumor is somatic or germline, it is necessary to sequence normal DNA from the same individual. While tumor-only WES data can be compared to large germline databases to infer whether a mutation is somatic, false positive calls are frequent, particularly in ethnic populations (Garofalo et al., 2016).

Sequence coverage: Mutation load and predicted neoantigens have rapidly emerged as standard biomarkers used in IO trials. The current gold standard laboratory assay for measuring mutation and neoantigen load is whole exome sequencing (WES; $n \approx 20,000$ genes), as opposed to whole genome sequencing (WGS) that provides additional information regarding noncoding somatic mutations that do not produce neoantigens. WES is therefore more cost-effective for immune-oncology purposes. Given that clinical genomics laboratories that are hospital-based or commercial more commonly use gene panels that cover dozens to hundreds of genes, questions have arisen whether these could be adequate for immunotherapy purposes. Dr. Garofalo and colleagues performed comparisons of gene panels with WES. Mutation loads were estimated using large ($n=300-500$) gene panels and were shown to correlate with WES mutational load above a certain cutoff, although by virtue of the limited sampling of human genes contained in gene panels, the vast majority of neoantigens could not be detected. Therefore, it may be concluded that gene panels are substantially inferior to WES in predicting neoantigens (Garofalo et al., 2016). For cost efficiency purposes, PACT will infer trunk versus branch mutations via allelic frequencies from a single tumor site versus multiple tumor sections.

Mutation calling: A recommended approach in the context of multicenter and multiyear clinical studies is to store raw NGS data files in secure databases and reanalyze all data simultaneously using a validated and harmonized pipeline to allow robust analyses of mutation and neoantigen loads with clinical and other data.

Copy number alterations (CNAs): CNAs, which include gains and deletions of DNA segments, can be detected using clinical WES (Rennert et al., 2016). While the relevance of CNAs in predicting the efficacy of immunotherapies is generally less understood, there are reports of specific CNAs correlating with immune phenotypes, and it will be informative to correlate CNAs with other immune markers.

Neopeptide prediction algorithms: Combined use of multiple tools likely gives a better prediction; however, more efforts are needed to accurately assess the immunoprotective properties of neopeptides.

Approximate Module Budget

This estimate is based on analyzing both tumor and normal samples from each patient.

The WES assay cost is \$500–\$1,100/sample (100x coverage, depending on the number of GB). The cost per patient may be estimated at \$2,200 if one assumes 100x WES with 9 GB. The PACT JSC will need to select the optimal coverage to cost ratio that will be acceptable for the WES Basic biomarker module.

Module 3a: Transcriptomic Characterization of Microenvironment

Transcriptional programs in the tumor microenvironment are an important downstream marker of biological processes such as T-cell activation with reported gene expression profile (GEP) signatures including Type I interferon, interferon gamma, T-cell exhaustion, Th1, as well as the cytolytic activity score. Signatures of extrinsic immune suppression such as IDO-1 or TGF-beta expression highlight mechanisms in addition to immune checkpoint blockade that may overcome resistance through combination therapy. In addition to signatures in tumor, pharmacodynamic changes in immune gene expression signatures in blood have been shown to correlate with response to treatment. Approaches to measure mRNA expression span low complexity techniques including qRT-PCR as well as medium complexity technologies such as TaqMan, Nanostring, Luminex, and targeted NGS panels via hybridization capture or PCR amplification, as well as genome-wide RNA sequencing. Several GEP signatures predictive of patient response to treatment have been reported: NanoString signatures in tumor have correlated with clinical outcome in patients treated with PD-1 blockade (Cesano, 2015; Geiss et al., 2008; Man Chow et al., 2016; Piha-Paul et al., 2016; Ribas et al., 2015). Whole transcriptome profiling provides the opportunity for genome-wide characterization of the TME.

Focus of the Project

The PACT team proposes to perform systematic RNA-seq at a depth of 150 million reads across all tumor samples.

In addition to profiling the primary tumor prior to treatment, profiling samples during treatment or upon relapse provides insight into mechanisms of resistance, and point to attractive combination opportunities; it is therefore suggested for those tumor indications where sequential biopsies are possible.

Value Proposition

Transcriptional read-outs of individual malignant and nonmalignant cells from tumor tissue may offer additional insights into cellular states and programs (and heterogeneity therein) that may influence response or resistance to cancer immunotherapies/combinations.

Through supervised or unsupervised learning, GEP modules can be identified and correlated with important clinical outcomes such as prognosis or response to treatment. There are ongoing clinical trials using NanoString GEP signature prospectively to triage patients for different immunotherapies. Novel genes that are co-expressed with established gene expression

signatures can identify new targets and illuminate unknown biology. Fingerprinting approaches can be used to deconvolute immune subpopulations. The expression of candidate neoepitopes can be investigated, as well as effects on alternative splicing.

Approximate Module Budget

The cost of these assays range from ~\$1,000–\$3,000, depending on the platform used for sequencing, the depth of coverage requested, and the type of RNA to be analyzed. Depending on the sequencing facilities and the number of samples to be analyzed, the average cost for a 150 million read standard RNA-seq should be approximately \$1,500/sample. This would make the estimated cost/patient ~\$1,500.

Module 4a: Liquid Biopsy - cfDNA

The difficulty in acquiring routine tissue biopsies in the solid tumor setting hinders the ability of a clinical laboratory to provide real-time information to clinicians and convenient options for patients. Advances across multiple areas—sample preparation, next generation qPCR and sequencing capabilities, rare cell detection and analysis, ultra-sensitive protein detection, storing, accessing, and analyzing very large data sets—are enabling unprecedented multi-dimensional data collection. Liquid biopsy for solid tumors is currently being used, but the complexity of integrating data across cfDNA, exosomes (includes profiling mRNA, miRNA, lncRNA, proteins, etc.), and circulating tumor cells poses a challenge to exploit the full potential of this approach. Moreover, advances in liquid biopsy technologies are occurring much more rapidly than clinical validation of these assays.

Focus of the Project

Biomarkers will be driven by the clinical questions asked. While it is not realistic to propose all possible clinical settings, it is highly likely that immunotherapies will continue to be combined with other targeted agents and therefore biomarker testing will reflect the combined mechanisms of action of all agents. For instance, in nonsmall cell lung cancer, EGFR mutations and ALK fusions will still be tested even as immune-related biomarkers are adopted. For this module, we are proposing a common approach in the pre-analytical phase of testing that will allow for better comparison of analytical testing platforms chosen by individual research teams.

NGS-DNA-seq will be the primary experimental screening platform, which is good for biomarker discovery/research, LDT approaches, and is also the preferred technology in specific settings (e.g., detection of minimal residual disease in certain heme malignancies).

Value Proposition

Testing specimens derived from relevant body fluids (e.g., blood, CSF, pleural fluid, etc.) that may reflect various aspects of tumor pathobiology could better enable clinical decision-making and provide for surrogate endpoints. It could also allow for broader immunoprofiling of patients at more time points before and after IO therapy. This ability to track data from IO treated patients longitudinally and more frequently will allow for more rapid development of novel IO-related biomarkers for treatment development and efficacy. PACT proposes as its basic biomarker module for liquid biopsy to conduct mutation analysis in cfDNA. Specimens for this assay and

other liquid biopsy options can be banked in a biospecimen repository for future processing. Again, this can provide for greater ability to immunoprofile patients using assays developed in the future.

Approximate Module Budget

The cost of this assay will be determined by the cost to collect and process the cfDNA, as well as the costs for the NGS-DNA-seq. The appropriate depth of coverage will need to be selected based on the clinical needs. A safe estimate may be ~\$1,100/sample to align with the WES costs from the DNA module. However, costs could be higher depending on the sequencing coverage required to find the desired mutations in the low amount of DNA present in these samples. The appropriate cost to coverage ratio will need to be determined by the JSC.

Value Proposition for the Basic Modules

Selecting a set of high importance, broadly applicable, and widely testable biomarkers that can be conducted for every PACT-related clinical trial will allow for the systematic cross comparison of IO therapy trial data on a much grander scale than is currently possible. This will allow novel precompetitive predictive biomarkers to be developed for IO therapies of various classes. The ability to cross-compare trials will also allow for complex modeling studies to be conducted to aid in the prediction of better therapy combinations. There are several key questions in the advancement of IO therapies that the biomarkers proposed by this initiative can attempt to answer. These include target engagement, pharmacodynamic activity, mechanisms of sensitivity and/or resistance, as well as identifying the most appropriate patients to treat based on risk/benefit criteria with individual agents or combination therapies. The value of having the data from all of these standardized assays for multiple clinical trials will be to accelerate the discovery of new immunoprofiling markers that can be used to hasten the approval for novel therapies.

Approximate Budget for Basic Modules

The current cost estimations for all the Basic biomarkers, including 3 peripheral flow panels, 1–2 basic IHC assays, WES, and RNA-seq for each patient, range from \$10,000–\$14,000 per time point. (Note: this is greater than the current estimated cost per patient for the CIMACs testing, which is ~\$8,000–\$10,000/sample.)

1.1.2 - Exploratory Module/Assay Development (Buy-up Options)

Evaluation of exploratory biomarkers may also can be performed depending on availability of samples from the periphery and tissue and the specific objectives of the relevant clinical trial. Various stakeholders (e.g., NCI or a company sponsor) can choose to fund these modules based on specific trial objectives or shared objectives across multiple studies. Importantly, exploratory biomarkers or novel assays are necessary for the continued evolution of the biomarker space and can graduate to become part of basic modules once better established. The proposed areas for exploratory marker development are listed below and described in detail in **Appendix 1**.

- ▶ Module 1c: Immune Cell Biology
- ▶ Module 2b: Cancer Genetics/Somatic Mutations

- ▶ Module 3b: Transcriptomic Characterization of Microenvironment
- ▶ Module 4b: Liquid Biopsy—CTC, cfRNA, exosomes
- ▶ Module 5: Defining the role of the microbiome in modulating CI responses
- ▶ Module 6: Non-Immune Cell Characterization of Tumor Microenvironment (differentiation, stroma, vasculature, etc.)

Value Proposition for the Exploratory Modules

Allowing expansion assays to be options for buy-ups for the PACT initiative will allow both the NCI and private sector to fund the development of additional assays that can then be validated to become basic modules that can be incorporated into future clinical trials. This will allow PACT to drive innovation of new IO biomarker development and allow end users to weigh in which biomarkers which markers should be developed. The value of executing these modules through PACT lies in the breadth of use of the markers that can be achieved across the community and the ability to generate consistent data in every trial. The PACT JSC can select and fund desired modules using an RFA or RFP process that insures buy-in and participation of both PACT partners and external trial sponsors.

Approximate Project Budget for the Exploratory Modules

The cost for these expansion modules will of course depend on which assays are selected to be developed and tested. The assay cost will depend the current maturity of the technology, the biomarkers to be developed, and the expense to fully test and validate them. The PACT team estimates an RFA for new biomarker development in clinical trials would cost ~\$1 million to \$2 million per biomarker, which would account for collection of enough data to analytically validate a new biomarker and potentially harmonize it to any existing data if necessary. Assuming development of each assay cost the maximum \$2 million, PACT would hope to fund development of at least one biomarker per year over 5 years for an estimated total of \$10 million for the RFA.

Project 1.2 — Creating a core laboratory network for biomarker analysis

Challenge/Opportunity

Although diagnostic tools have significantly enhanced the depth and comprehensiveness of our abilities to characterize the tumor immune microenvironment, the current use and development of translational biomarkers are limited by insufficient resources for large-scale studies, variabilities in pre-analytic/analytic qualities and standards, and, more importantly, by a lack of common standards and platforms for biomarker data collection (especially for nongenomic “immune” parameters) and inadequate computational tools/platforms for complex, high dimensional analysis.

Consequently, at least three elements are critical to enabling optimized biomarker strategies:

- ▶ Access to biospecimens from early and late stage single agent and combination clinical trials that involve relevant immunotherapy agents
- ▶ Access to laboratory resources and assays with analytical validation and standardization appropriate for achieve clinical biomarker testing
- ▶ Availability of suitable, interoperable data repositories for clinical, genomic, and non-genomic data generated across disparate trials and organizations, similar to that provided by the NCI Genomic Data Commons

Solution

PACT proposes to build on the Research Funding Announcement (RFA) released by the National Cancer Institute (NCI) in November, 2016, to establish a **network of Cancer Immune Monitoring and Analysis Centers (CIMACs) and a Cancer Immunologic Data Commons (CIDC)**, in order to provide consistent, standardized biomarker assays and data repository for NCI's extramural clinical trial networks (links to RFAs in **Appendix 5**). The RFA is open to application from academia, nonprofit and for-profit organizations, and up to 3 CIMACs will be funded with a total budget of \$32.5 million for all 3 centers from NCI over 5 years starting 2017. Each CIMAC will encompass a multidisciplinary group capable of a wide range of analyses for genomic, phenotypic, and functional characterization of the tumor immune system using analytically validated and standardized platforms. The CIMAC-CIDC network will function in a coordinated manner through a central Core Laboratory Coordination (CLC) Committee. The capacity of the proposed CIMACs will provide the mechanism and basic infrastructure needed for objectives of **Program Area 1** of the PACT initiative.

- ▶ The CIMACs to be established through the RFA are budgeted to address the biomarker study needs of early clinical trials of immunotherapy that use the NCI clinical trial networks. PACT has the potential to leverage components of this infrastructure for PACT-prioritized studies. For example, PACT can add new capacity for specific assay platforms or expand the scope of biomarker work for more clinical trials and patients selected by PACT.
- ▶ The clinical trials for PACT-supported biomarker studies can be conducted through a variety of existing clinical trial infrastructures supported by NCI, academia, nonprofits, and industry.
 - ▷ For example, the NCI Cancer Therapy Evaluation Program (CTEP) has an extensive extramural clinical trial network for phase 0 to phase IV trials [including ETCTN, NCTN, the Cancer Immunotherapy Network (CITN) and the Children's Oncology Group (COG)]. CTEP provides standing support for centralized regulatory, data collection, drug distribution infrastructures, and clinical trial conduct in the network sites. CTEP also has a large portfolio of immunotherapy and targeted agents under its collaborative agreements with multiple pharmaceutical companies. Since 2010, CTEP has initiated more than 90 phase I to phase III trials for immunotherapy agents and novel combinations involving immunotherapy.
 - ▷ Other clinical trial mechanisms would also be appropriate for PACT-supported biomarker studies, such as academia, nonprofit funded immunotherapy consortia, and industry-sponsored trial networks.

- ▶ Private sector diagnostic and assay companies and laboratories will be eligible to compete to conduct certain assays for the CIMACs if the CLC determines that this is the most efficient way to conduct these tests.
- ▶ PACT will identify existing/planned trials or develop new trials using existing trial mechanisms and support the implementation of biomarker studies in order to address important scientific questions prioritized by the PACT JSC (as described in Project 2.1 and PACT Governance).
- ▶ PACT will facilitate and maintain close communication with industry, academia, and non-profits for their inputs in identifying opportunities and gaps, prioritizing scientific projects, and sharing expertise and resources where appropriate. This effort is delineated in Project 2.2, described below.

Focus of the Project

To support the goals of the proposed PACT Program Area 1, a network of reference labs will be identified for high priority assay platforms. These “core” biomarkers to be applied are described in Project 1.1. Depending on the stages of development of specific markers and the anticipated purposes of their uses in trials, varying degrees of analytical validation will be required (defined in Project 1.4).

Proposed services for biomarker studies may include quantitative and qualitative methods for immunoprofiling using phenotyping, functional analysis, genomics, epigenomics, transcriptomic, proteomics, metabolomics, or glycomics. Although Clinical Laboratory Improvement Amendment (CLIA)-certified assays are not required for all biomarker studies to be supported by PACT, the selected core laboratories should have the capacity to carry on validation steps from analytical to clinical validation for candidate markers and perform integral biomarker assays (for treatment eligibility) in a CLIA-compliant laboratory that may require an Investigational Device Exemption (IDE) from the FDA. Assay platforms to be employed by reference labs may include, but are not limited to:

- ▶ Multi-spectral flow cytometry, mass cytometry and imaging cytometry
- ▶ DNA-seq for genotyping of variants, T-cell clonality, relevance of T-cell and B-cell epitopes
- ▶ High-throughput transcriptional profiling, RT-PCR, NanoString, RNA-seq
- ▶ Pathological and morphological imaging techniques (e.g., confocal microscopy)
- ▶ Immunohistochemistry (IHC), multiplexed immunofluorescence

The scientific goals of the lab network are to search for patient/treatment selection markers and provide mechanistic insights into immunotherapy agents and combinations. In appropriately selected clinical trials, specific biomarker objectives may include, but are not limited to:

- ▶ Defining the role of inflammation and tumor microenvironment in response/resistance
- ▶ Phenotypic and functional characterization of the immune system, and its impact on response/resistance

- ▶ Functional genomics of tumor and host
- ▶ Identifying tumor target antigens, such as neoantigen, and responding host T-cell receptor repertoire
- ▶ Developing assays to guide rational selection of combinations in individual patients
- ▶ Longitudinal sampling to monitor dynamic changes and target modulation by drug (e.g., in combination therapy)
- ▶ Defining the role/impact of the human microbiome on response/resistance
- ▶ Exploring the mechanisms and predictive markers of immune-related toxicities

A few guiding principles will be followed in the selection of the reference laboratories:

1. The network of laboratories should have the collective capabilities to carry out comprehensive immune profiling assays and analysis on clinical specimens. Based on the current understanding of relevant biomarker platforms, core and exploratory immune biomarker modules are described in Project 1.1, although the lists of the two categories may evolve with time.
2. Depending on the stage of scientific and technical development, some markers will be best tested in individual labs (such as markers utilizing newly developed technologies, and exploratory biomarkers). Others will be developed within a network of qualified labs (such as markers with existing standards and harmonization, and basic biomarkers) or a single high-capacity facility (for certain selected platforms and markers, including both basic and exploratory biomarkers).
3. Each reference lab should participate in, and agree to, the following assay validation and delivery standards:
 - ▶ Adherence to key performance metrics (to be defined) including data quality management systems; development and provision of standardized IO assays using standardized protocols and methods; and banking, tracking, and distribution of biological samples in a compliant manner that would allow dissemination to clinical practice
 - ▶ Delivery of data in standardized formats, for example, in:
 - ▷ IHC: e.g., intensity scores, percent tumor cells at each intensity, H-score, special locations
 - ▷ Next Generation Sequencing (NGS): e.g., BAM files, VCFs
 - ▷ Other scoring methods/algorithms: e.g., immune cell infiltration patterns
 - ▶ Routine, regular performance reviews focused on quality, proficiency testing, and compliance

Value Proposition

The establishment of a network of reference labs will enhance the efficacy, quality, and power of biomarker analysis across immunotherapy trials. By applying standardized sample processing and assay protocols, deviation of test results due to pre-analytical and analytical variations will be minimized, allowing for cross-trial comparisons. Systematic incorporation of key biomarker modules will expand the power of individual trials through combined analysis with other trials.

Approximate Project Budget

The estimate costs for this project is based on the NCI budget for CIMACs, as well as the PACT basic biomarker cost estimates:

(b) (4)

The PACT funds raised to synergize with the CIMACs effort from NCI will:

- ▶ Cover the expenses of the PACT-initiated biomarker projects within PACT selected trials.
- ▶ Expand the testing services of the existing CIMAC network formed from NCI funding to establish assays for biomarker studies in trials prioritized by PACT.
- ▶ Add new assays or platforms to existing capacities.
- ▶ Add new labs with specialized capabilities of novel technologies or expand the general capabilities of the network.

Project 1.3 — Creating a database for all PACT biomarker data

Challenge/Opportunity

A pre-competitive common database or data access platform is particularly important for immunotherapy biomarkers, since individual trials, even large Phase III trials, may not have sufficient power for complex correlative analysis. However, there currently is no widely available repository that contains biomarker data for IO; instead multiple databases are being implemented without coordination and therefore without consistency. Because IO biomarker research is a nascent field, there is a huge opportunity to ensure early data harmonization

and standardization optimization. The definition, collection, storage, and sharing of data and metadata from multiple sources must be standardized: reproducibility of research results and the ability to broadly translate findings will be impossible without such standardization. The data types to be collected, and the adoption or creation of open standards for storing them need to be determined.

Solution

NCI and NIH already have programs to establish unified data repositories that enable data sharing across cancer genomic studies and that are made accessible to the scientific community, such as the Genomics Data Commons (GDC). Construction of both an Imaging Data Commons and a Proteomics Data Commons is also actively proceeding. An NCI Cancer Immunologic Data Commons (CIDC) is in the planning stages and is a natural extension of this concept, and the timing of this effort aligns well with the PACT initiative. Analysis will need to be performed to determine the appropriate model for such a repository, e.g., whether it makes more sense to create a single database to which contributors send their data, or to use a federated model, where researchers can access, combine, and analyze the data as it is acquired from multiple sources. Once a model is defined, collection mechanisms will be created to ensure the data are obtained in a fashion that does not require double or duplicative data entry. This resource will also need to have the capability to house or access corresponding patient level clinical data, i.e. diagnosis, key demographics, treatment history, and outcome history. This feature will be absolutely critical in order to make the resulting biomarker information truly useful.

Another key component for the PACT database will be that contribution of data will be mandatory for all NCI led trials; however, it is understood that for company-driven trials, participating may be limited by the presence of proprietary information. Company sponsors would therefore be allowed to limit the outcome data placed in the repository as necessary. A staged approach will be needed for implementation.

There are multiple NCI programs that have potential relevance to this Project 1.3:

- ▶ **NCI programs where large amounts of relevant data are being collected** already exist and can be leveraged for PACT.
- ▶ CTEP supported Clinical Trial Networks (as mentioned in Project 1.1). The NCI provides significant resources to the CTEP infrastructure. The NCTN grants a total of approximately \$150 million/year for trials, and the ETCTN grants a total of approximately \$20 million/year for trials. In addition, NCI also issues support contracts (CTSU, CIRB, etc.) for both total that total approximately \$60 million/year. In short, this means that during the first 5 years of PACT, the NCI will invest ~\$1.1 billion/5 years or ~\$230 million/year to conduct clinical trials. Many of these trials are currently studying IO agents or combinations with IO agents. Data generated from some CTEP trials may be used for standardization and harmonization and serve as the initial population of the CDIC.

- ▷ The Quantum Immuno-oncology Lifelong Trial (QUILT) is developing a Master Protocol, and the blanket consent can be adopted to allow the data generated to be broadly shared.
- ▷ The NCI Center of Excellence in Immunology's (CEI) mission is to foster discovery, development, and delivery of novel immunologic approaches for the prevention and treatment of cancer and cancer-associated viral diseases. The CEI collaborates with the CITN, partners with the Society for the Immunotherapy of Cancer (SITC), and fosters collaborations with Biotech and Pharma.
- ▶ **NCI and private sector efforts to develop platforms for immunological data deposition, integration and/or analysis will help guide the CDIC design efforts.**
 - ▷ NCI has an initiative to establish a CIDC (a U24 mechanism RFA is in the planning stages), which would serve as a bioinformatics core center for research data collection, analyses, integration, and data sharing for studies completed by the CIMACs. This effort can be leveraged as the starting point/prototype for the Immunological Data Commons as well as for the data generated by the CIMACs. The short-term goal for this project is to collect and integrate data to allow within- and cross-trial analyses for NCI network studies. The longer-term goal is to provide a common platform to make the data accessible by the IO community and to allow integration with data from outside the NCI. This platform could be used to create common analysis pipelines, as has been done in the GDC for genomic data.
 - ▷ Platforms already exist for various data types or data integration (within industry, nonprofits, data/diagnostic companies, and academia). One example is ImmPORT, The Immunology Database and Analysis Portal, a partnership between researchers at the University of California-San Francisco, Stanford University, the University of Buffalo, the Technion-Israel Institute of Technology, and Northrop Grumman. It is funded by NIAID. ImmPORT can serve as a model for data integration.

Potential synergies between other ongoing efforts and PACT can be used to enhance both programs.

- ▶ Public/private partnerships, which can be leveraged to gain momentum and agreement on issues including the development and use of data standards, data sharing agreements, and the actual sharing of data that is being generated.
 - ▷ Global Immunotherapy Coalition (GIC)
 - ▷ Parker Institute for Cancer Immunotherapy
 - ▷ Bloomberg-Kimmel Institute for Cancer Immunotherapy

- ▶ Complementary projects, where efforts can be made to integrate with varied types of data (genomic, clinical, proteomic, imaging) and to accelerate the discovery and the development of new treatments
 - ▷ NCI Genomic Data Commons & Cancer Genomics Cloud Pilots—focused on genomics data harmonization and accessibility and analysis
 - ▷ NCI Imaging Data Commons (early-stage planning)—focused on imaging data harmonization and accessibility
 - ▷ NCI Proteomics Data Commons (early-stage planning)—focused on proteomics data harmonization and accessibility
- ▶ Other agencies
 - ▷ FDA development of standards for submissions of immunological biomarker data and related documentation designed to support potential regulatory marketing authorization, if applicable
- ▶ Standards development organizations
 - ▷ Clinical Data Interchange Standards Consortium (CDISC), including possible use of Study Data Tabulation Model (SDTM)
 - ▷ NCI Metadata Thesaurus and Cancer Data Standards Repository (caDSR)
 - ▷ Biomedical Research Integrated Domain Group (BRIDG), which is part of ISO
- ▶ Clinical trials conducted by other networks and companies
 - ▷ External trials may not utilize the same assays and platform as PACT studies but would still be useful to include in the database if there was sufficient information about the biomarkers employed to determine analytical validity.
 - ▷ Bridging or compatibility studies would need to be conducted for these trials, and data harmonization would need to be done. These tasks have been accounted for in the budget for this project.

Focus of the Project

Project 1.3 will:

- ▶ Develop a database platform—a “data commons”—that includes both published and unpublished data, to enable data sharing.
 - ▷ Selection of a database technology will need to account for the inchoate nature of this work, providing flexibility and mechanisms to standardize, store, integrate, and interrogate new types of data that will be generated. Clinical, safety, and biomarker data should be contained or accessible through one source. As much as possible, data to be collected should be defined up-front, with the understanding new data types will follow.

- ▶ Identify or enhance data collection tools for the types of biomarker data collected from the basic and expansion biomarker modules defined in Project 1.1, while concurrently developing new tools and data collection standards that may be needed for certain data platforms.
 - ▷ The biomarker data platforms will likely include tumor genomics, T-cell receptor sequencing, RNA-seq and NanoString, IHC or multiplex IF, flow cytometry, cytokine panels, and functional analysis.
 - ▷ As available, additional patient-level data will be included in the database to be paired with the biomarker data, such as diagnosis (e.g. cancer site, histology, staging), patient demographics (e.g. age, gender, race), treatment (e.g. medications, start / stop dates), and outcome history (vital status, disease status, relevant ancillary medications).
- ▶ Provide or develop tools to access and analyze the data and mechanisms to inform clinicians and basic and translational researchers of the challenges of drug combinations and how to optimize treatment for patients.
- ▶ Identify software to support data collection from participating institutions and integration of that data into the data commons.
 - ▷ Role-based security that takes into account HIPAA and FISMA requirements and a variety of authorization models must be an integral part of the system.
- ▶ Identify barriers to data sharing/transparency amongst various drug development parties and develop strategies to overcome those barriers.

Value Proposition

The goal of this project is to create a means to collate, maintain, harmonize, share, and curate the IO data collected in PACT-participating clinical trials, as well as any basic and translational research data that the PACT initiative may identify and request to be contributed to the database, such as that from PACT Program Area 2. The Cancer Moonshot Blue Ribbon panel has specifically called for a “national infrastructure” as a core component of the CITN, and that success will be measured by new, effective treatments “in more patients, across many different cancers.” Achieving this goal requires the ability to integrate and analyze multiple data types from a wide variety of sources. In addition to providing an IO biomarker database for the initial set of clinical trials, the ultimate goal of the repository is to provide access to the research community and enable analyses of the complex systems biology data, which will drive the more systematic and data driven selection of IO combination therapies. This will allow for more efficient drug trials to be conducted by companies and hopefully eliminate duplicative efforts across the field.

Approximate Project Budget

The estimated budget for this Project is based on the NCI Cancer Genomics Cloud Pilot costs and assumes we will be building upon existing resources.

(b) (4)

(b) (4)

1. \$10 million—Acquire storage and compute resources for database platform. Analysis needs to be performed to determine if in-house or cloud-based infrastructure is most appropriate. Security, Authentication, and Authorization components will be developed. Ongoing operations, maintenance, licensing, and leasing costs are included.
2. \$4 million—Develop a database platform, or “data commons,” that includes both published and unpublished data to enable data sharing. PACT will identify the appropriate data model, leveraging existing resources (e.g., NCI Thesaurus) wherever possible and work with community experts to define appropriate data models where standards do not already exist.
3. \$2 million—Identify or enhance data collection tools for the types of biomarker data prioritized to be collected from the basic and exploratory biomarkers defined in Project 1.1, while concurrently developing new tools and data collection standards for certain platforms. This will require establishment of data standards where they do not currently exist and will dovetail with Item 2 above.
4. \$2 million—Develop software/mechanisms to support data submission by participating institutions and integration, validation, and QA of that data in the CIDC.
5. \$2 million—Identify or develop tools to access and analyze the data and mechanisms to enable clinicians and basic and translational researchers to understand the promise and challenges of specific drug combinations and how to optimize treatment for patients. The PACT team understands that this amount will likely not be enough to fully develop all the tools necessary for these endeavors; however, the \$2 million will kick-start the development/enhancement of tools, which could also additionally be funded by grant programs such as Informatics Technology for Cancer Research (ITCR), as well as by private interests. In addition, it is recognized that having a critical mass of data available will be a catalyst for the community to start using it and improving upon existing tools.

This would supplement the \$1 million/year in the CIDC RFA for a total of \$30 million/5 years for both public and private sector funding.

Project 1.4—Assay standardization and validation for high priority basic biomarkers

Challenge/Opportunity

Biomarkers to improve the efficacy of immunotherapy for cancer patients are important tools in clinical management and drug development. Comprehensive profiling of the tumor immune interface with multiparametric technologies that encompass the dimensionality and complexity of the interaction of the tumor and the immune system is needed to monitor and stratify cancer patients for individual therapeutic requirements. A number of candidate biomarkers and platforms with the potential to be developed into assays to predict response to immunotherapy or monitoring have been identified in Project 1.1. The analyses are typically accomplished

through various laboratory assays to measure differences in specific tumor and immune parameters before, during, and after treatment. This may allow the identification of tumor and immune signatures, which correlate with immunotherapy response or resistance or immune related adverse events, and select patients for treatments using the biomarkers, including those identified in Project 1.1.

The diversity of reagents and approaches used in current IO research has produced a large variety of methodologies that are being used to assess the immune systems of humans and data reporting procedures that are frequently not consistent. This situation often hampers data reproducibility among laboratories, which hampers meaningful interpretation of results across studies and could lead to selection of different intent to treat populations. In addition, most of the assays used involve high-throughput multi-parametric “signatures” that require considerable statistical and bioinformatic efforts for proper algorithm development and robust data interpretation. Such capabilities are not currently available to all investigators assaying immune biomarkers and, therefore, biomarker testing is not consistently or uniformly being performed in academic or clinical laboratories due to resource constraints. Furthermore, there is no existing system that can easily integrate analyses across different clinical trials. Given these challenges, which others in the IO field have further detailed (van der Burg et al., 2011), assay standardization will be a critical focus of the PACT effort.

Different approaches to overcome these limitations and to address different technical and logistical challenges have evolved in the process of standardizing biomarkers. The importance of using standard guidelines for both specimen acquisition and analytical methods for biomarker measurements is widely recognized. First, biomarker measurements in clinical trial specimens should use high-quality, fully specified and validated assays. Second, the assay results should be comparable among clinical sites within a trial and between different trials. These goals may be achieved through use of central labs, assay standardization, harmonization, or concordance testing:

- The creation of validated assays with the kind of consistent pre-analytical, analytical, and post-analytical processes required for inclusion into clinical trials can be achieved through the **use of central laboratories** and a centralized biospecimen repository. A central laboratory that is affiliated with the entity sponsoring the trial offers the potential advantages of using the same validated assay to screen all patients and ensuring responsiveness and familiarity with the clinical trial. In addition, flexible, close communication between clinical and research teams during assay validation can be important elements for success in making a biomarker assay viable for use across different studies. Centralized testing provides assurance about the performance of a test, and minimizes differences in test performance or result reporting that can confound the definition of the intent-to-treat population within and across clinical trials. The ability to offer testing at central laboratories allows for integrated testing, sample management, and data-management services, which can facilitate efficient and reliable biomarker testing and data delivery as part of the comprehensive biomarker characterization.

- ▶ An alternative approach that facilitates the comparability and integration of data across multiple laboratories is **assay standardization**. Assay standardization and traceability to reference materials insure the most accurate and meaningful test results. Standardization also makes interpreting laboratory results easier for the physicians providing patient care. Because each assay can have its own reference interval, physicians currently must be able to apply the same reference interval to each test performed by a specific laboratory in order to accurately interpret that laboratory's results and to be able to compare across laboratories. With standardization, analytical results are more likely to be similar across all testing methods so that only one reference interval is needed, significantly decreasing the burden currently placed on physicians in interpreting laboratory results. Standardization is not a one-size-fits-all proposition. It requires development of standard unit measurement definitions, consistent calibration points, and standardized primary and secondary reference methods and/or materials for each analyte.
- ▶ Since reference materials and standards do not exist for many protein and nucleic acid analytes, **harmonization of biomarker assays** is another approach. Harmonization allows for the establishment of assay-specific protocols in individual laboratories while minimizing differences in assay performance due to assay-related variables. The use of identical reagents, instrument platforms and/or protocols and scoring criteria across laboratories is one solution, but this may not be feasible across many different laboratories. The harmonization process involves the participation of multiple laboratories in a consortium-based iterative testing process to identify the variables crucial for assay performance. To begin, individual laboratories participate to perform parallel quality control experiments on replicate samples with assay proficiency panels using the labs' own reagents, instrumentation, and protocols. A central laboratory manages logistics for the proficiency panel, receives raw and analyzed data sets from each participating laboratory, and provides independent central data analysis. During initial proficiency panels, variables are identified that impact test performance across the labs. Subsequent independent panels are then used to optimize protocols and harmonize the assay-related variables across laboratories (van der Burg et al., 2011).
- ▶ An example of an effort that addressed **concordance testing** or a comparability approach across multiple IHC-based PD-L1 tests was the Blueprint PD-L1 IHC Assay Comparison Project, which is a collaboration between the International Association for the Study of Lung Cancer, American Association of Cancer Researchers (AACR), four pharmaceutical companies (Bristol-Myers Squibb, Merck & Co. Inc., AstraZeneca PLC, and Genentech/Roche), and two diagnostic companies (Dako/Agilent and Ventana/Roche). Further detail and other examples of harmonization projects are in **Appendix 2**.

Solution

A part of methodological improvements for tumor and immunoprofiling assays provided in PACT will involve the creation of validation guidelines for immunoassays to support immune biomarker application and development for clinical trials. Part this project will enable the standardization and validation of assays to interrogate the IO biomarkers identified in Project 1.3. Standardization

and validation of the assays to be used for multisite trials and across different trials should minimize variability in assay results and provide an opportunity for comparability across sites and studies. Achieving a high level of data reproducibility and data comparability will help to accelerate the development of therapeutics targeted to specific biomarker-selected patient populations.

Focus of the Project

This project will likely have two aspects: 1) assay standardization/harmonization and 2) establishment and distribution of standard operating procedures (SOPs) and best practices.

1. Assay standardization/harmonization

First, 1–2 core laboratories from within the core laboratory network will be selected to validate existing assays for the PACT basic biomarkers. These laboratories should be able to establish technically and analytically validated assays that include several continuous steps of biomarker development. Technical and analytical validation refers strictly to the performance of the assay. Assay clinical validation occurs as part of the outcome analysis in clinical trials that ensures that the assay performs robustly according to predefined specifications (fit-for-purpose) that will establish acceptable criteria for use in future studies. Clinical utility, which refers to establishing the use of a biomarker test leads to a favorable benefit-to-risk balance, that is, guides clinical decisions that lead to better outcome, should also be planned.

PACT projects can be tasked to address various aspects of assay validation and standardization for selected markers based on the PACT JSC recommendation:

- **Evaluation of pre-analytic factors:** An important step in biomarker validation is the evaluation of **pre-analytical factors** that may affect assay performance due to specimen-related variability. For immunotherapies, for example, there may be a need to monitor *ex vivo* immune responses in phenotypical or functional assays, which require high-quality samples to ensure reliable analytic output. To ensure that optimal pre-analytic processing regimens are followed, SOPs for controlling specific biomarker development steps are essential. In general, best practice metrics can be defined for various parameters depending on the specimen type to be used. For instance, protocols for blood collection and processing, tumor collection, sample fixation and processing, and storage media optimization are often developed. To improve standardization of specimens, NCI has published best practice guidelines for biospecimen collections (National Cancer Institute, 2011). PACT will endeavor to follow these published guidelines where possible and make modifications where needed. Additionally, pre-analytical considerations for certain assay types can be found in **Appendix 2**.
- **Technical and analytical validation:** Analytical validation involves establishing the performance of an assay for its intended biomarker measurement. Analytical validation studies can include 1) accuracy, 2) precision, 3) analytical sensitivity, (4) analytical specificity, 5) reportable range of test results for the test system, 6) reference intervals (normal values) with controls and calibrators, 7) intersite reproducibility if the assay is to be performed in multiple laboratories, and 8) establishment of appropriate quality control measures (Becker,

2015; Jennings, Van Deerlin, Gulley, & College of American Pathologists Molecular Pathology Resource Committee, 2009; Landis & Koch, 1977; Linnet & Boyd, 2012; Mandrekar & Sargent, 2009). There are also validation study considerations depending on the type of assay and specimens that are used. For example, reader precision studies are needed for IHC tests, whereas molecular assays require accuracy studies. Whether the assays are for integral, integrated, or exploratory biomarkers, they must be fit-for-purpose and meet the acceptable criteria defined for the intended use in patients and trials. PACT will be able to use samples from trials that participate to perform technical validation of assays, when deemed necessary and approved by the trial sponsored.

- **Clinical validation:** After an assay has been analytically validated, PACT-associated laboratories may also be able to carry out **clinical validation** of the assays to determine whether the assay result has a clinically meaningful correlation with the condition of interest—for example, whether the assay reliably divides the patient population(s) of interest into distinct groups with divergent expected outcomes to a specific treatment. The laboratories will be asked to perform assays for integral biomarkers (for treatment eligibility) in a CLIA-compliant laboratory, and use of the test in a trial may need to be performed under an IDE from the FDA if it is a significant risk trial. This aspect will not be a requirement of all PACT-associated laboratories.
- **Assay harmonization and concordance testing:** For certain biomarkers and assay platforms, there may be a need for assay harmonization between labs or testing of concordance between validated assays. Such projects will be prioritized by the PACT Joint Steering Committee depending on the scientific importance or the clinical trial needs of PACT to have these assays become part of the basic biomarker modules and uniformly performed across all PACT-associated trials.

2. Establishment and distribution of SOPs and best practices.

The PACT core laboratory network group will create a **committee** to coordinate efforts and to promote synergistic research efforts among the core laboratories. This Core Laboratory Committee (CLC) will meet monthly and review to progress in developing biomarker assays and report its findings to the PACT JSC. It would operate as a work group of the JSC, but would remain a separate entity reporting to controlled by the NCI CIMACs. The CLC will select best practices from the CIMACs and generate and distribute SOPs and other materials among the core laboratories to keep the assays standardized and updated with best practices. These SOPs and materials will be shared with external partners that wish to run the PACT modules in their trials and contribute their data, but not use the PACT core laboratory network.

Evaluation and prioritization of biomarkers and platforms for which validation will be required will be assessed by the PACT JSC.

Value Proposition

The biological complexity of the tumor and immune system interaction poses multiple challenges associated with technical development of clinically applicable assays when evaluating different variables as markers of clinical benefit to immunotherapy. However, each of the potential biomarkers and their associated assays requires high-quality validation in order to be used effectively in clinical applications. Considering the increased relevance and emphasis on biomarker development in cancer immunotherapy, there is an enormous need to facilitate and improve the steps to demonstrate clinical value of molecular diagnostics in this space. PACT will apply standardized approaches for biomarker validation described above, when necessary, to enable more efficient assay development to identify IO-relevant biomarkers, which are crucial to guide personalized therapy and for advancing IO options for cancer patients.

Approximate Project Budget

The cost of this project will be tied to the time and resources necessary to establish an analytical performance of each assay. Because flow cytometry, IHC, DNA/RNA sequencing, and other analytical methods constitute a large segment of the molecular characterization of the tumor and immune profiling, they will likely be the first validated for specific use. The estimated cost for running each assay for validation is \$500–\$1,000/sample, depending on the assay type (~\$500/sample for IHC versus ~\$1,000 for some flow cytometry panels), with the likely need to perform comprehensive analysis of 100 samples to validate any assay head-to-head. Cost for one assay comparison would then be ~\$50,000–\$100,000. For more complex assays, there could be additional costs even beyond this estimation. There would also be additional costs associated with time of the technical staff, biostatistical staff, and computer scientists for stand-up of the assays within the labs and the postanalytical phase of assay validation. The hope is that these costs could be partially defrayed since the CIMACs will already be established. In addition, PACT would hope that the cost for the samples for these validation assays would also be low due to the availability of banked samples in the PACT biorepository.

Project management and organizational support for the panel and team will also be required in order to assemble and keep current the materials for the drafting and review of the SOPs. A small team to do this—contracted separately from the core laboratory network and including one project manager and one science writer at full-time salary and benefits, plus the meetings and supplies—would cost ~\$400,000/year.

The following table summarizes the total budget for Program Area 1:

Program Area 1 Consolidated Budget

| PROJECT PLAN SECTION | BUDGET ITEM/ PROJECT GOAL | (b) (4) | TOTAL PROJECT COST |
|--|--|---------|--------------------------|
| Project 1.1.1 and 1.2 | Create core laboratory network to conduct biomarker assays | (b) (4) | (b) (4) |
| Project 1.1.2 | Develop new IO biomarkers | | |
| Project 1.1 and 1.4 | Expand biorepository capabilities for sample storage | | |
| Project 1.3 | Create database to bank IO biomarker data from clinical trial | | |
| Project 1.4 | Standardize and harmonize biomarker assays for IO therapy | | |
| PROGRAM AREA 1 | | | \$205.75M |
| Program Area 1 — “Buy-up” Option ► Supplement to defray costs of additional tissue collection at clinical sites | | | |

Program Area 2: Provide scientific coordination for the selection of clinical combination therapy trials important to the field but not already being performed elsewhere, and co-fund such trials with partners

Project 2.1 – Landscape analysis and literature review of biomarkers being developed and IO and other therapy combinations being tested across the oncology field

Challenge/Opportunity

One of the primary hurdles the PACT initiative will face is that the field of IO is moving at such a rapid pace compared even with other portions of the cancer research and clinical fields. This accelerated pace of research, drug development, drug release, and clinical use of IO therapies will make it challenging for PACT to select which biomarkers to develop and test unless these deliberations are accompanied by a “real time” effort to gather information on all of the current trials and related activities in the field. Specifically, the Scientific Project Selection Panel (SP²) and Joint Steering Committee (JSC) will need guidance on which biomarkers and combination therapies are being tested or are in development. A crucial piece to development of this guidance will be to produce it quickly as the timeline will need to parallel the IO drug development pace.

Solution

To stay current and synergize most effectively with other efforts in the IO and oncology field, we propose to have a small team of science researchers and writers regularly conduct a landscape analysis of critical efforts in the IO field. The first fully comprehensive landscape analysis will occur just after the launch of the PACT initiative. This comprehensive analysis will likely take approximately 1–3 months to fully research all publically available information about ongoing biomarker and combination trials within the IO space that have taken place to date, and then compile that data into a digestible format for the SP² for review. This group will also engage with PACT company members to acquire data on the emerging company trials, as well as to gain any organizational insight into the IO landscape that can assist in the selection of combination therapies and biomarkers to be addressed through PACT.

The landscape analyses will include publically available data from publications, websites (e.g., clinicaltrials.gov and others), abstracts, and corporate websites and publications, as well as insights gleaned directly from conversations with relevant industry representatives, both PACT and non-PACT members as appropriate. Both public and private information will be collected, and the FNIH (or its contractor) will act as a neutral third party to collect the data. Two versions of a summarized report will be generated: 1) a high-level summary devoid of any proprietary data, which can be reviewed by the entire PACT JSC to assist in decisions, and 2) a more detailed summary which may include some proprietary data—as necessary and if willing to be shared—to be reviewed only by the SP² (which, it should be recalled, will include no members of competing pharmaceutical companies, but only academics and ex-company members with no conflicts of interest). The authors of the landscape analysis as well as the SP² members will be bound by confidentiality agreements.

From this analysis, the team will create and maintain an up-to-date summary clinical trial compendium for combination therapies and biomarkers in development from current and emerging data across the entire IO space enabling categorization of trials into three types: 1) highly relevant to the entire IO field, funded trials; 2) proposed trials that are highly relevant to the IO field but currently unfunded; and 3) trials of low relevance. The SP² will review this compendium and use it to make recommendations to the JSC about which trials and resulting biomarker modules PACT should pursue, and which trials PACT should help to co-fund. As a secondary feature, the SP² will also be able to make recommendations to the IO outreach team about which groups to work with to develop cross-fertilization efforts and which other groups to approach about depositing their trial data into the PACT database for harmonization with PACT biomarker modules.

After this initial landscape analysis is generated, it will be shared with the appropriate governing bodies for PACT to allow them to make their initial decisions. A landscape update will be conducted biannually each year the PACT initiative continues. These biannual updates will take place in the month immediately following the annual meeting for the American Society of Clinical Oncology (ASCO) and the European Society for Molecular Oncology, which usually occur in early summer and late fall. These meetings usually have the largest release of data from all stakeholder groups relevant to the PACT initiative and therefore will be ideal targets for the landscape updates. While these meetings will be the primary target for data review due to the large amounts of new data released, the analysis will also be sure to account for data released at other meetings in the time between landscape scans, such as the ASCO, American Society of Hematology, American Association of Cancer Research annual meeting, and others. After each update, a report similar to that generated after the initial landscape analysis will be prepared and shared with appropriate committees.

Value Proposition

A full picture of current and upcoming biomarker testing will allow the PACT teams to continuously update its pipeline of basic and exploratory biomarker modules. Having the most current list of IO combinations being tested will also allow the PACT initiative to approach

the right individuals with whom to discuss incorporating their markers and trials into PACT, and help construct a knowledge base to help guide the field with respect to choosing future combination studies.

The landscape analysis will also help support the active outreach to other groups that are working in the IO space described as part of Project 2.2.

Approximate Project Budget

(b) (4)

The total cost for this project is therefore estimated at ~\$1 million dollars over the 5 years.

Project 2.2 – Selection of trials with high-priority combination therapies and biomarkers for co-funding by PACT

Challenge/Opportunity

As mentioned above, PACT will not establish its own clinical trials network infrastructure or fully sponsor and conduct the trials itself (i.e., contract with selected clinical sites; finance and monitor patient accruals; hold INDs; conduct safety reporting; submit registrations etc.), but will work with existing trial networks to implement clinical trials that will use the PACT biomarker modules. These clinical trials may come from the NCI's clinical trial networks (e.g., ETCTN, NCTN, CITN, and COG), industry, academic investigator-initiated trials, or nonprofit consortia (e.g., Stand Up 2 Cancer, Parker Foundation IO Consortium), provided groups are willing to work with PACT and implement the biomarker modules within them. Partner trials will be selected by the PACT JSC based on the landscape analysis described in Project 2.1 after review by and based on the recommendations of the SP². JSC will next work with an outreach project team from FNIH to help broker a partnership for PACT biomarkers on those trials and eventual deposition of the data into the common database. This outreach project team could also encourage companies or other trial networks to initiate new trials using some of the high-priority combinations identified by the SP² if these trials are not currently in the pipeline. (This is further described in the description of Project 2.3 below.) The PACT team also recognizes there will be a few particularly high-value combination trials to be conducted that need some supplemental funding in order to be launched, as they may not be within the short-term pipeline of any company. PACT will work

to facilitate partnerships between the necessary companies to initiate these trials, PACT can consider providing supplementary funding to conduct these trials through mechanisms already available, or it may choose to institute a unique RFA mechanism for these trials.

The following are some examples of how this will work:

- ▶ **Example 1: PACT initiates new trials for novel combinations and supports the relevant biomarker studies:** A new high-priority treatment or combination regimen is identified by the SP², and the JSC decides it should be a PACT trial because the biomarker and clinical objectives would fill critical gaps in the field. However, the companies with the compounds of interest are not able to prioritize their resources to fund the clinical and biomarker studies in their entirety. (Or, alternatively, PACT proposes new trials for combinations already in clinical testing, but finds that additional studies with alternate designs or clinical settings are needed (e.g. with pharmacodynamic endpoints or biomarker stratifications) to address critical biomarker or clinical questions not otherwise tested.) In this case, PACT approaches the companies and offers to help support the costs of the biomarker testing. The size of the trials may range from small phase I/pilot studies to larger phase II trials. As an example, one could estimate a trial of 50 patients to cost ~\$6 million. PACT could invest ~\$2 million to conduct the biomarker assays and some site supplements. If the trial were to be conducted through the CTEP infrastructure, CTEP would supplement payments to trial sites to cover ~\$2 million. This would then leave the companies with only ~\$2 million to raise to conduct the trial. It is the hope that this reduced cost would incentivize the companies to participate in the trial as part of PACT.
- ▶ **Example 2: PACT supports biomarker studies in ongoing/planned trials:** The SP² identifies an existing clinical trial involving immunotherapies that are suitable for high-priority biomarker studies, and the JSC decides it would fit well as a PACT trial. However, the companies sponsoring the trial are only able to conduct limited biomarker assays. In this case, the PACT team will approach the sponsoring companies (or clinical trial network, depending on the trial structure) and ask them to collect samples to run at least the basic biomarker modules in their trial. In this case, PACT pays for the testing of these biomarkers only. If one assumes this is a phase I/II trial with a cohort of 50 patients, then the PACT supplement for this trial would consist of \$500,000 to conduct the biomarkers plus an additional \$500,000 to supplement collection and storage of the additional samples needed for the biomarker testing. This would result in a total of an approximately \$1 million trial supplement. Trials of this type could come from either the NCI Clinical Trials Networks or from the private sector.
- ▶ **Example 3: PACT supports biomarker studies in completed trials:** The SP² identifies a clinical trial of a high-priority therapy combination or biomarker objectives that has already been conducted and for which properly banked biospecimens are available, and the JSC decides it would fit well as a PACT trial. PACT funds the conduct of basic biomarker modules on the samples. (This may be phase I, II, or III trials.) The cost to run the basic biomarker modules would be tied to the number of patient samples. If the trial collected 200 patient samples, the cost would be ~\$2 million to run the basic biomarker assays.

As noted in each of the examples, once drug combinations of interest or existing clinical trials are identified and the decision to provide PACT support has been made, the PACT outreach team from Project 2.3 will work to recruit the necessary partners. In addition, as the PACT program develops, a mechanism can be established for teams to send proposals for priority combination therapy trials to the JSC for review independent of the landscape analysis.

Value Proposition

Co-funding trials through PACT will enable trials that would not normally be conducted by companies on their own, but that have high potential value to the field, to be conducted, with the resulting data shared with the research community. Co-funding could also be a means to conduct retrospective biomarker assays on banked samples from high-priority data that would substantially add to our understanding of the science behind IO and related combinations.

Approximate Project Budget

Costs for this project will be partially accounted for in the biomarker budget for Project 1.1, as one of the main aspects of co-funding will be to pay for testing of the biomarkers for the trials. However, it is anticipated that there will also be a need for funding for an RFA to support 5–10 of the highest-priority trials to be conducted during the first 5 years of PACT. It may also be possible to create an RFA for clinical trials through either the ETCTN or NCTN. (b) (4)

(b) (4)
(b) (4)
(b) (4) Co-funding could range from simple biomarker support to partial trial funding. The RFA could be administered either through FNIH or NCI depending on the desired needs and structure of the partnership.

Further PACT Trial Co-Funding (Optional)

The amount for co-funding detailed here represents an initial investment by PACT to assist in getting important trials conducted. (b) (4)

(b) (4)
(b) (4) This further funding can be determined in future years and on a trial-by-trial basis with the funding partners if the PACT model proves to be successful.

Project 2.3 – Active outreach and coordination with other ongoing IO/oncology efforts

Challenge/Opportunity

As a logical counterpart of its biomarker development, assay standardization, data integration, and trial (co-)funding mission, PACT is designed to serve as a clearinghouse and coordination point for information and insights on potential IO and combination therapy research. Given this PACT will need to coordinate actively with the many existing and emerging public and private research efforts in the field.

Solution

A scientific program management team at FNIH and experienced in facilitating the work of public- private partnerships will leverage the information from the landscape analyses that are ongoing in Project 2.1 to conduct targeted outreach and establish external collaborations with similar programs supported by biopharmaceutical companies, nonprofits, academic medical institutions and government agencies. This team will work to coordinate efforts continuously across all active IO efforts, avoid duplication, share information, and ultimately meet the PACT objective of a systematic translation, evaluation and validation of biomarkers and assays.

Value Proposition

A proactive, constant outreach to and involvement of other IO/combination efforts will allow the most efficient use of the investments of PACT stakeholders and there sources available in the field, given biological complexity of immunotherapies and related combinations and the breadth and depth of what must be learned in order to deliver effective treatments to patients.

Approximate Project Budget

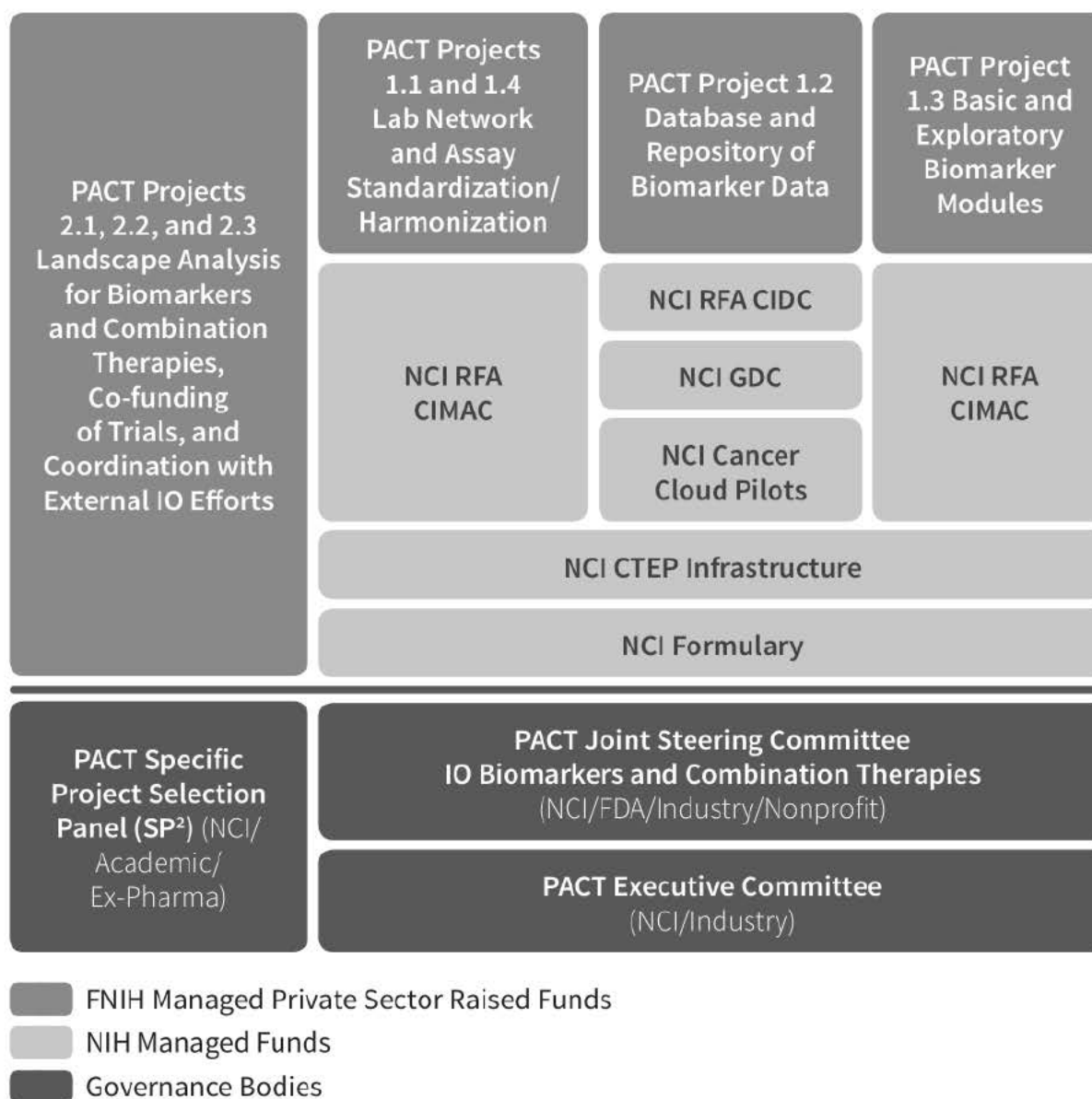
(b) (4)

The following summarizes the total costs to support Program Area 2:

Program Area 2 Consolidated Budget

| PROJECT PLAN SECTION | BUDGET ITEM/ PROJECT GOAL | (b) (4) | TOTAL PROJECT COST |
|--|--|---------|--------------------|
| Project 2.1 | Conduct biannual landscape analysis to determine priority biomarkers and combination therapies | (b) (4) | (b) (4) |
| | Compensate SP ² members for trial and biomarker landscape review | | |
| Project 2.2 | Co-fund high-priority combination clinical trials | | |
| Project 2.3 | Conduct outreach and coordinate with other IO efforts | (b) (4) | (b) (4) |
| PROGRAM AREA 2 | | | |
| Further PACT Trial Co-Funding (Optional) ► Additional funding for specific clinical trials and biomarkers, which can be decided on a trial-by-trial basis | | | |

PACT Governance



To achieve its objectives, PACT will require a governance structure that 1) maintains close involvement by both public and private partners in key decisions; 2) protects confidential or proprietary information and guards against conflicts of interest; 3) provides both continuous strategic direction for the partnership and rigorous operational management of its different component parts; and 4) enables timely decision-making, avoiding unnecessary bureaucracy. To accomplish these goals, we propose four **focused governing bodies to run the partnership**:

1. An operationally focused PACT Joint Steering Committee (JSC), each member of which will direct different aspects of the PACT research plan.

2. A PACT Scientific Project Selection Panel (SP²) to analyze existing and potential therapeutic and biomarker studies and make recommendations regarding which biomarker studies could be executed as part of PACT. This will be an advisory rather than decision-making body. The JSC will make the actual selection of which trials should be part of PACT based on the SP²'s recommendations.
3. A PACT Executive Committee (EC) to provide high-level strategic direction, communication with the top leadership of each of the partner organizations, and resolution of general policy issues. The EC will oversee the actions of the JSC and the SP² and communicate with other PACT partners via an Extended Executive Group, consisting of senior executives from partner organizations not actively serving on the EC.
4. In addition, a PACT Patient Advisory Committee (PAC) will be added to the governance structure of PACT upon the launch of PACT years 4-5, consisting of representatives from cancer patient advocacy organizations. The PAC will periodically review the progress of PACT and provide input to the EC and JSC on PACT's relevance to and support of cancer patient needs and concerns.

PACT Joint Steering Committee (JSC)

Execution of the research programs in PACT will be governed through a JSC composed of members from participating companies, government agencies, and nonprofit organizations. The JSC will operate under the direction of the PACT Executive Committee (EC).

The responsibilities of the JSC will include:

1. Reviewing the recommendations of the PACT SP² (described below) and using these recommendations to set operational research priorities for PACT programs, including selecting the optimal combination therapy trials for PACT partnerships.
2. Reviewing the progress of projects on an ongoing basis and adjusting project plans to ensure appropriate tradeoffs between the timely achievement of key project milestones and production of quality results. The JSC is therefore the primary forum for discussion among the PACT partners of potential operational changes to the final research plan, based on emerging opportunities and challenges, and within the context of the project budgets.
3. Meeting regularly with the Core Laboratory Committee (CLC) to ensure lab coordination and development and distribution of SOPs and best practices.
4. Conducting assessments of key project milestones, including critical go/no-go milestones, and communicating these assessments to the EC.
5. Determining how private sector funds provided to FNIH are distributed (consistent with the final research plan).
6. Working with the potential PACT PAC, which will be composed of patient advocates.

7. Reviewing the results of the research efforts under PACT and making recommendations regarding how they are disseminated and publicized, consistent with NIH publication rules.
8. Overseeing active outreach to, and coordination with, other related cancer research and trial efforts as described in Project 2.3 (above).

While the final overall research plan for PACT will be decided jointly by NIH/NCI and industry partners, the funds provided by NIH and industry for PACT will flow through separate streams. NIH funds must be disbursed according to NIH procedures for solicitation of applications, review of applications, and decision-making. NIH will have final statutory decision-making authority over the conduct of its grants, as provided in the federal regulations, although private sector partners will have the ability to provide input on the progress of the NIH-funded research through the JSC.

Private sector partner funds will be contributed through and managed by FNIH. (FNIH will also coordinate any material in-kind private sector contributions to PACT.) Such funds may be dispersed directly by FNIH through grants or contracts, or transferred by FNIH to NIH for disbursement through NIH grants. The JSC will review and select proposals made directly to FNIH for funding. After awards are made, the JSC will provide project oversight for all studies, whether funded by NIH or industry/FNIH, in a manner consistent with NIH procedures as described above.

The membership of each of the JSC will be as follows:

- ▶ Three to four NIH members (voting), including program officials for the relevant NIH grants
- ▶ At least one representative from FDA (nonvoting)
- ▶ One voting representative from each funding industry partner; additional industry representatives may attend as alternates but will be nonvoting
- ▶ One voting representative from each nonprofit organization that matches company funding levels for PACT
- ▶ Subject matter experts, such as academic investigators, whether funded by PACT or not; may be added at the JSC's discretion, but will be nonvoting
- ▶ At least one representative from FNIH (ex-officio, nonvoting)

The JSC will be co-chaired by one NIH and one industry representative, selected by the PACT EC, but who is not part of the EC.

After the projects are launched, the JSC will meet regularly (likely monthly) via teleconference, and at least twice yearly in person. The frequency of meetings will be adjusted as the scientific agenda requires. The JSC may also convene smaller “working groups” of experts that include PACT stakeholders to advise on specific areas of science or technical aspects of the research plan. The decisions of the JSC will be made by simple majority. Each participating company will have one vote as will each qualifying nonprofit partner, and the resulting private sector cumulative

vote will remain constant at 50 percent of the total votes. If additional industry members are added to the partnership, votes for all industry participants will be scaled appropriately. NIH will have votes that will not exceed 50 percent of the total. The goal of the JSC will be to drive consensus on partnership decisions. In the unlikely event that this cannot be achieved, any conflicts will be raised to the EC for resolution. JSC operational logistics, staffing, and project management will be managed by FNIH.

PACT Scientific Project Selection Panel (SP²)

Some of the most important decisions made in the course of PACT involve choosing appropriate studies or projects to execute using the PACT infrastructure or with PACT funding. These include consideration of which biomarkers or preclinical models to develop, around which drugs or drug combinations these efforts should be focused, and—for Program Area 1 (biomarkers)—which clinical trials should be selected to have biomarker studies executed in PACT (Program Area 2). We expect that proposals to execute combination clinical trials with biomarker studies defined in the modules within PACT will be of several different types:

1. A proposal for a biomarker “companion study” to be run using an NCI-sponsored (ETCTN or NCTN) trial as a “backbone,” where samples and clinical data collected from such trials are run through the PACT infrastructure.
2. A proposal to test combinations brought to PACT by one or more industry partners, where samples and data collected from these trials would be developed using the PACT core labs.
3. External sponsors of individual trials could also choose to run PACT biomarker modules using PACT-developed assays and standard SOPs in labs they select outside the PACT core labs and contribute data back to the NCI Data Commons.

Evaluating studies that are proposed to run under PACT or which datasets to accept into PACT will require significant scientific expertise, potential access to sensitive or confidential company data (such as proposed trial protocols, results of point of care or early-phase preclinical or clinical studies, investigator brochures), and the ability to provide objective recommendations that are based on the science rather than individual commercial considerations. In this regard, the JSC will need to rely on advice from a separate panel of oncology experts who are knowledgeable about oncology (with a particular focus on IO) and who have practical experience in biomarker and therapeutic development, but can provide objective advice and are free of conflicts of interest with regard to the interests of specific companies. PACT will establish the SP² to fill this advisory role.

The SP² will determine which potential therapeutic combinations and which biomarkers have the highest priority for assessment in the PACT infrastructure. The SP² will oversee the conduct and distribution of the landscape analysis described in Project 2.1 above and will use information from the landscape analysis and other sources to identify candidate studies for PACT. FNIH will provide research services (through a subcontracted consulting group if needed) to collect

the background information needed to assess these studies. FNIH (or its subcontractor) will execute the necessary confidentiality agreements with companies and other entities whose studies are being considered by the SP² and with individual SP² members to ensure proprietary or confidential information is used only to support PACT decisions and is protected from inappropriate disclosure. The SP² will focus on combinations that address currently unmet needs for the field and for patients (i.e., are not effectively being tested elsewhere) and that offer a compelling scientific rationale for inclusion in PACT and make specific recommendations to the JSC about which studies to pursue. The SP² may also communicate its most general findings more broadly where they may be of use to specific sponsors or to the oncology community.

The membership of the SP² should include the following:

- ▶ NCI scientists and medical officers with expertise in PACT interest areas. This may include one or more members of the JSC who can act as liaisons.
- ▶ FDA scientists.
- ▶ Academic researchers with relevant clinical and translational research expertise. These members, while they serve on the panel, will not be able to serve as principal investigators on studies associated with PACT.
- ▶ Scientists with industry experience in oncology drug development who do not have current employment with or active ties to individual companies in the areas of interest for PACT, to avoid conflicts of interest.
- ▶ One or more representatives from nonprofit/patient organizations with an interest in IO.

The SP² will meet at least quarterly (or more often if needed) by teleconference. Two of these quarterly meetings will be set to correspond to the completion of the twice yearly landscape analysis updates. The SP² will be co-chaired by one NIH and one academic researcher and will report to the PACT EC. Each member will have one vote; decisions will be made by simple majority. In the unlikely event that consensus cannot be achieved, conflicts will be raised to the EC for resolution. SP² operational logistics, staffing, and project management will be managed by FNIH.

PACT Executive Committee (EC)

The PACT EC will be responsible for oversight of PACT, ensuring that the partnership overall is conducted efficiently and in the best interests of patients and the public health, and for communicating the value of PACT to its partners and the public. Specifically, the EC will be responsible for the following:

1. Providing general guidance for the overall strategy of PACT within the rapidly changing oncology landscape.

2. Reviewing the progress of PACT on a regular basis and ensuring its effective and timely execution. This includes review and approval of major go/no-go milestones and funding changes.
3. Communicating the progress of PACT and any related challenges to the partners and the oncology community, and managing the relationships among the partners.
4. Establishing the policies that govern PACT and ensuring they are adhered to.
5. Overseeing the operation of the PACT JSC and SP², and resolving any conflicts or questions that they may not be able to resolve on their own.
6. Considering new initiatives or partners that may be added to PACT over time.

The membership of PACT (voting, except where otherwise noted) will include the following:

- ▶ The Director of the National Cancer Institute (or the Director of the Division of Cancer Treatment and Diagnosis) at NCI's discretion
- ▶ The Deputy Director of NCI
- ▶ The Director of CTEP, Division of Cancer Treatment and Diagnosis, NCI
- ▶ Two representatives from FDA (representing both CDER and CDRH)
- ▶ A patient advocate representative
- ▶ Three senior-level executives from three different biopharmaceutical company partners (head of research and development or global head of oncology research or development)
- ▶ A representative from the NIH Office of the Director (ex-officio, nonvoting)

The EC will be co-chaired by one senior official from NCI and one senior executive from one of the industry partners. It will meet at least quarterly by teleconference and will seek opportunities to meet periodically in person as schedules allow. Voting will be by simple majority.

To insure effective communications with and input from all PACT stakeholders, an Extended Executive Group, consisting of the EC members and representatives from the private sector partners not currently included on the EC, will be established to receive regular updates on PACT and advise the EC on its progress and direction. The Extended EC will meet twice a year by teleconference. The EC and the Extended Executive Group will be convened and supported by FNIH.

Consolidated Total Budget Estimate

The following table summarizes the budget inputs from Program Areas 1 and 2 into a single high level view of the total PACT budget:

| CONSOLIDATED ITEMIZED PACT BUDGET | | | | |
|--------------------------------------|---|---------|--------------------------|---------|
| ALL COSTS REFLECT TOTAL OVER 5 YEARS | | | | |
| PROJECT PLAN SECTION | BUDGET ITEM/ PROJECT GOAL | (b) (4) | TOTAL PROJECT COST | (b) (4) |
| Project 1.1.1 and 1.2 | Create core laboratory network to conduct biomarker assays | | \$102M | |

| CONSOLIDATED ITEMIZED PACT BUDGET | | | | |
|--------------------------------------|--|---------|--------------------------|---------|
| ALL COSTS REFLECT TOTAL OVER 5 YEARS | | | | |
| PROJECT PLAN SECTION | BUDGET ITEM/ PROJECT GOAL | (b) (4) | TOTAL PROJECT COST | (b) (4) |
| Project 1.3 | Create database to bank IO biomarker data from clinical trials | | \$40M | |

*Indirects lower for this project because a majority of work will occur at NCI and not academic institutions.

| CONSOLIDATED ITEMIZED PACT BUDGET | | | | |
|--------------------------------------|--|---------|--------------------------|---------|
| ALL COSTS REFLECT TOTAL OVER 5 YEARS | | | | |
| PROJECT PLAN SECTION | BUDGET ITEM/ PROJECT GOAL | (b) (4) | TOTAL PROJECT COST | (b) (4) |
| Project 1.1.2 | Develop new IO biomarkers | | \$40M | |
| Project 1.4 | Standardize and harmonize biomarker assays for IO therapy | | \$11.25M | |

| CONSOLIDATED ITEMIZED PACT BUDGET | | | | |
|--------------------------------------|---|---------|--|--------------------------|
| ALL COSTS REFLECT TOTAL OVER 5 YEARS | | | | |
| PROJECT PLAN SECTION | BUDGET ITEM/ PROJECT GOAL | (b) (4) | | (b) (4) |
| | | | | TOTAL PROJECT COST |
| Project 1.1.2 and 1.4 | Expand biorepository capabilities for sample storage | | | \$12.5M |
| PROGRAM AREA 1 | | | | \$205.75M |
| Project 2.1 | Conduct biannual landscape analysis to determine priority biomarkers and combination therapies | | | \$1.15M |
| | Compensate SP ² members for trial and biomarker landscape review | | | \$0.5M |

| CONSOLIDATED ITEMIZED PACT BUDGET | | | | |
|--------------------------------------|---|---------|--|--------------------|
| ALL COSTS REFLECT TOTAL OVER 5 YEARS | | | | |
| PROJECT PLAN SECTION | BUDGET ITEM/ PROJECT GOAL | (b) (4) | | (b) (4) |
| | | | | TOTAL PROJECT COST |
| Project 2.2 | Co-fund high-priority combination clinical trials | | | \$27M |
| Project 2.3 | Conduct outreach and coordinate with other IO efforts | | | |
| PROGRAM AREA 2 | | | | \$28.65M |
| FNIH Program Management Costs | | | | \$16.6M |
| PACT Initiative Total | | | | \$251M |
| Program Area 1—"Buy-up" Option | | | | |
| Program Area 2—"Buy-up" Option | | | | |

Appendices

Appendix 1: Exploratory Biomarker Modules – Detailed Description

Evaluation of unknown biomarkers can be performed depending on availability of samples from the periphery and tissue and specific objectives of the relevant clinical trial. Various stakeholders (e.g., National Cancer Institute or company sponsor) can choose to fund these modules based on specific trial objectives or shared objectives across multiple studies.

Module 1c: Immune Cell Biology

As a potential expansion to the study of the immune cell biology to develop novel biomarkers, the PACT team suggest single-cell sequencing of tumor cells and immune cell subsets on a small number of tumors, such as myeloid-derived suppressor cells (MDSC), tumor-associated macrophages (TAM), neutrophils, T-cell clonality, and the use of newer technologies such as NanoString and CyTOF imaging, can be used to understand immune cell characterization, cell trafficking, and spatial co-localization of multiple cell types in the tumor microenvironment (TME).

Focus of the Project

Tumor and Periphery

- Analyze and compare different immune cell populations in the tumor and periphery (blood) by immunohistochemistry (IHC) and flow cytometry (or CyTOF) with standard operating procedures and quality-controlled experiments. Examples of potential markers are listed in Table A-1.

TABLE A-1: EXAMPLES OF CELL POPULATIONS

CELL POPULATIONS/MARKERS (EXAMPLES)

T cells (e.g., CD3, CD8, CD4, CD45RO, FoxP3, TIM3, LAG3, PD1, etc.)

NK cells (e.g., CD5, CD16, etc.)

B cells (CD19, activation markers, etc.)

Macrophages (e.g., CD163, CD206, CD64, etc.)

Dendritic cells (e.g., CD11c, CD1c, CDC141, HLA-DR, ILT7, etc.)

MDSCs (e.g., OLR1, CD15, CD14, etc.)

Neutrophils

Mast cells

Eosinophils

- ▶ Use similar marker set for flow cytometry and IHC, when possible:
 - ▷ Have multiple methods assessing same markers to ensure quality data.
 - ▷ Flow cytometry allows for quantification of immune cell subsets.
- ▶ IHC allows for analysis of localization of different immune populations (e.g., in T-cell- rich/ poor areas, edge, etc.).
- ▶ Depending on sample size, ability to do multiple panels will allow evaluation/quantification of larger number of markers than IHC. Will need to propose prioritized panels if sample is limiting.
- ▶ Functional cell analysis (e.g., T-cell and MDSC assays).
- ▶ Compare immune cell subsets in blood versus tumor.
- ▶ New assay formats allowing visualization of the 3-dimensional immune architecture of selected larger tumor samples (perhaps from pre-operative trials/window of opportunity trials) could be explored. This would expand knowledge obtained from standard IHC (Gerner, Kastenmuller, Ifrim, Kabat, & Germain, 2012; Gerner, Torabi-Parizi, & Germain, 2015).
 - ▷ Program infrastructure (clinical and bioinformatics) should be established with a view that technology combining assessment of molecular markers in the context of tumor (maybe tumor-draining lymph node as well) spatial architecture will evolve and will need to be incorporated in the future.

Module 2b: Cancer Genetics/Somatic Mutations

There are at least three high-priority expansion biomarkers that should be considered for answering specific questions related to DNA analysis: copy number alterations, single-nucleotide polymorphisms (SNP), and T-cell-receptor (TCR) and B-cell receptor (BCR) deep sequencing. Each of these should be employed as called for in relation to the mechanism of action of the therapy being tested.

Single-Nucleotide Polymorphisms (SNPs)

While still exploratory, germline SNPs that are associated with autoimmune disease may be useful to predict response or adverse events in cancer immunotherapy. One approach is to use SNP arrays to characterize established autoimmune markers. For example, genome-wide association studies have identified hundreds of SNPs associated with autoimmune diseases such as rheumatoid arthritis, lupus, and multiple sclerosis (Gregersen, Diamond, & Plenge, 2012). Immuno-oncology (IO) therapies alter the state of the immune system within the TME, and a major limitation is autoimmune adverse events. SNP genotyping will determine if the genetic predisposition to autoimmune disorders is predictive of response to IO therapy or adverse events. Ninety-five percent of 612 SNPs associated with 21 common autoimmune diseases can be genotyped using a combination of two commercially available SNP chips (MEG and Immune) from Illumina. These chips could be enhanced with additional SNPs associated with less common autoimmune disorders observed as adverse events during IO treatment.

TCR and BCR Deep Sequencing

Advances in genome sequencing technologies have also enabled the development of a new powerful platform for probing the adaptive immune systems (immunosequencing). Millions of TCR or BCR sequences can be read in parallel from a single sample by immunosequencing for the quantification of T- and B-cell clonal response in peripheral blood and tumor. The clinical application of immunosequencing for the diagnosis and monitoring of lymphoid malignancies demonstrated high sensitivity and specificity. The presence of tumor-infiltrated lymphocyte (TIL) correlates with a favorable clinical outcome. Emerging data suggest that both the number of TIL and degree of specific clonal expansions in pretreatment melanoma samples are predictive of response to anti-PD-1 therapy (Tumeh et al., 2014). TCR repertoire in peripheral blood correlates with immune-related adverse events in patients treated with immune checkpoint blockade. Immunosequencing biomarkers have the potential to help guide dose regimens and combination therapies. Moreover, for adoptive T-cell transfer or chimeric antigen receptor T-cell therapy, immunosequencing is used to identify novel tumor antigen/neoantigen-specific TCR and monitor the therapy itself by tracking the injected T cells. Immunosequencing has opened many avenues with the breadth of potential application in immunotherapy.

Module 3b: Transcriptomic Characterization of Microenvironment

Emerging technologies are making significant progress in characterizing the primary and acquired resistance mechanism for patients. Challenges include potential changes in RNA during the formation of single-cell suspensions that are required for current scRNA-seq protocols, low capture efficiency of cellular transcripts (10–15% using 3' poly-A capture), and limited sensitivity that makes detection of low-abundance transcripts unreliable. RNA-seq analysis of single functional cytolytic T cells with various immune phenotype markers provides additional information about the impacts of different molecules on cytolytic function, potentially to explore their correlation with clinical outcome.

Focus of the Project

Single-cell suspensions can be obtained from tumor samples where the tissue is processed with or without enzyme digestion, with a need to establish cell freezing media under a standard operation procedure.

No single marker will serve the purpose of transcriptomic characterization of the TME. Therefore, the main focus should be on comprehensive measurements of multiple baseline and on-therapy markers that are related to response and resistance to IO agents. Some of the currently available readouts include the interferon gamma signature, the cytolysis score, and mesenchymal or stemness tumor phenotype.

Experimental Screening Platforms To Include and Purpose for Each:

- ▶ Whole-transcriptome profiling via next-generation sequencing (NGS) is recommended with baseline profiling at a minimum, and longitudinal samples for tumor indications where available are strongly encouraged.

- ▶ Peripheral blood mononuclear cell profiling is also recommended.
- ▶ Application of emerging single-cell characterization techniques are suggested to be explored and incorporated.

Emerging tissue processing approaches such as those that recover single nuclei for RNA-seq provide an opportunity to characterize immune subpopulations with unprecedented specificity. One advantage of single-cell techniques compared with bulk profiling is that the molecular features of rare subpopulations can be extracted and may help to identify novel targets. Another advantage is that one can clearly assess the relative frequencies of the various subpopulations such as T cells, T-regulatory cells, MDSCs, and TAMs.

In addition to providing an opportunity to characterize specific immune subpopulations within the TME, single-cell profiling can resolve cell subpopulations that are obscured by whole-tissue transcriptome profiling as well as their associated gene expression patterns and dynamics, and quantify cellular heterogeneity within a tissue, peripheral blood, fine-needle aspirate, or bone marrow aspirate.

Value Proposition

It is important to characterize the primary and acquired resistance mechanisms for patients who fail to respond to immune checkpoint blockade monotherapy, or transiently respond and then progress afterward. Transcriptomic profiling is one approach to identify these resistance mechanisms and guide combination clinical strategies, and can also be used to assess the impact of drug treatment to identify or validate pharmacodynamics markers of response.

Module 4b: Liquid Biopsy – Circulating Tumor Cells (CTCs), cfRNA, Exosomes

Focus of the Project

For the expansion biomarker module for liquid biopsy, we will look to develop techniques for better analyzing CTCs, cfRNA, and exosomes.

Experimental Screening Platforms To Include and Purpose for Each:

- ▶ Quantitative polymerase chain reaction (qPCR) – research tool that is readily translatable into commercial and regulatory viable *in vitro* diagnostic
- ▶ NGS – RNA-seq – good for biomarker discovery/research, laboratory-developed test approaches; also may be preferred technology in specific settings (e.g., detection of minimal residual disease in certain heme malignancies)
- ▶ Epic Biosciences and Rarecyte CTC platforms – selection agnostic CTC approaches; broader potential across many tumor types
- ▶ Exosome collection and subsequent DNA/RNA sequencing methods

Module 5: Defining the Role of the Microbiome in Modulating Cancer Immunotherapy Responses

Determinants of response to checkpoint blockade are under intense research and are likely to include immunosuppressive status in the TME as well as systemic priming status of the immune system.

Microbiome biomarker development is an active area of research that has already yielded intriguing results that have not only associated microbial population changes with oral, pancreatic, and colon cancer, but may also yield clues regarding the molecular mechanisms linking microbial interactions with these and other types of tumors (Linares, Gustafsson, Baquero, & Martinez, 2006; Schloissnig et al., 2013).

At present, there are no human datasets linking microbiome changes with anti-tumor responses. However, some intriguing recent preclinical studies suggest that the microbiome is required for the anti-tumor activity of anti-PD-L1 and anti-CTLA4, as these antibodies lack their efficacy in mice devoid of microbiota, and the efficacy is transmissible to poor-responder mice via the microbiota. Although we are at a very early stage in this field, these animal studies suggest that systemic immunity is in part regulated by the microbiome.

Value Proposition

Since human data are fundamental to start to address the role of the microbiome in cancer immunotherapy, we propose to stimulate prospective studies in patients undergoing immunotherapy. The principal activity will focus on bacterial communities measurable in fecal samples. Potentially, this project could be expanded to include multiple microbial communities across different mucosal surfaces.

Microbes as Biomarkers

Well-characterized and validated biomarkers of disease can be used for cancer detection and diagnosis, or to measure patient response to therapeutics, and may also provide a rationale for choice of therapy.

The importance of developing microbiome-based patient phenotypes is supported by recent studies demonstrating that when gut bacterial communities are compromised, immunotherapy and standard chemotherapy regimens may lose efficacy (Iida et al., 2013; Viaud et al., 2013). Thus, a detailed knowledge of each cancer patient's unique microbiome could have high translational value to clinical practice since this information could be exploited for the purposes of optimizing individual therapeutic responses, possibly by altering microbial signals to change host metabolic regulation or by developing new metrics for patient stratification based upon matching therapeutic agents with an individual's microbial metabolism or immune profile.

Focus of the Project

Depending on the clinical application, microbiome-based biomarkers may be developed by examining various features and readouts, alone or in combination with existing biomarkers. For example, advanced *in silico* techniques have been used to analyze individual metagenomic profiles as a molecular biomarker that may identify pathogenic or drug-resistance collective phenotypes (Zackular, Rogers, Ruffin, & Schloss, 2014).

Indeed, a current clinical trial (NCT02141945) is testing a metagenomic-based diagnostic tool for patients with colonic neoplasia.

Other strategies have been devised to associate specific tumor/microbe interactions that include the following:

- ▶ Analysis of whole-organism presence/abundance
- ▶ Detection/quantification of biosynthetic products (outer membrane vesicles, miRNA, toxins, lipopolysaccharide [LPS])
- ▶ Detection/quantification of microbial metabolites (short-chain fatty acids [SCFAs], 2-HG, bile acids)
- ▶ Molecular signatures of host responses to altered microbiomes

Thus, colonic hyperpermeability and pro-inflammatory cytokine profiles that are associated with specific bacterial taxa could be used to identify individuals at risk for disease progression or poor therapeutic response.

Potential biomarkers that PACT could expand to test are:

- ▶ Levels of bacterial taxa (16S sequence data)
- ▶ Levels of bacterial metabolites (SCFAs, bile acids, etc.)
- ▶ Levels of bacterial enzymes (β -glucuronidase (GUS), bile acid hydrolases, etc.)
- ▶ Levels of serum LPS, muramyl dipeptide
- ▶ Host inflammatory cytokines/host molecular signatures of dysbiosis

Experimental Screening Platforms To Include and Purpose for Each:

- ▶ Enzyme activity screens (480-well) for detecting bacterial enzyme levels
- ▶ Microarray or enzyme-linked immunosorbent assay for detecting cytokine profiles
- ▶ High-throughput mass spectrometry for detecting bacterial metabolites
- ▶ Quantitative immunohistochemistry for detecting immune checkpoint receptor levels after probiotic treatment

Module 6: Non-Immune Cell Characterization of Tumor Microenvironment (Differentiation, Stroma, Vasculature, Etc.)

Tumor resistance and immune evasion are influenced tremendously by the surrounding nonimmune microenvironment that can include stromal cells, blood vessels, and small particles (e.g., exosomes, ectosomes, microvesicles), cytokines, and enzyme or adhesive properties that are derived from these. These have distinct roles based upon the type of cancer (solid tumor versus hematologic disseminated tumor) and intrinsic driving tumor biology.

Focus of the Project

PACT could use the following as a starting point for expansion biomarker modules:

- ▶ Small particles (exosomes, ectosomes, microvesicles) from blood and the TME.
- ▶ Antibodies that selectively separate mesenchymal stromal cells from tumor and hematopoietic immune cells and strategies to isolate these for single-cell molecular characterization.
- ▶ Markers of blood vessels (i.e., CD34, CD31 and endoglin), effective angiogenesis, and tumor hypoxia and strategies to accurately quantitate these in relevant models.
- ▶ The representative nonimmune cell genes (DNA and RNA) could be used to assess the signature of vasculature, stroma, and other nonimmune cells in the TME. It is of importance to explore their correlation with tumor and immune cell-derived signature in the same tumor, as well as clinical outcome.
- ▶ Baseline serum vascular endothelial growth factor (VEGF) demonstrated the correlation with clinical outcome in melanoma patients treated with CTLA-4 blockade.
- ▶ Combination anti-VEGF with checkpoint blockade showed better clinical response in patients with melanoma and renal cell carcinoma.

Experimental Screening Platforms To Include and Purpose for Each:

As small particles and their contents will be mixed in blood, technologies that separate these based upon distinct antigens expressed by the releasing nonimmune microenvironment cells will be important.

If canine models of spontaneous cancer are chosen to study this, it will be necessary to establish the reagents compatible with exosome (and other small particle separation) and also IHC and separation strategies for other types of stromal cells.

Imaging strategies that allow examination of intracellular exosomes and their trafficking along with adhesive properties of tumor and stromal cells will be important.

Support of a comprehensive center to study this in the setting of spontaneous canine tumors or another large animal model will be needed.

Value Proposition

While features related to tumor vasculature and angiogenesis have been extensively studied and therapeutics directed toward this successfully, our understanding of the other components of the nonimmune microenvironment is at an elemental stage. Furthermore, animal models available to study this are very limited. An opportunity to study these interactions comes potentially from the many solid and hematologic spontaneous mouse models and also companion canine models of cancer where serial sampling of tumors can occur and sufficient blood volume can be obtained to study soluble factors as well. Early clinical data showed that combination immune checkpoint blockade with the agents to overcome nonimmune-cell-derived suppression potentially achieved a synergistic, favorable clinical response.

Appendix 2: Additional Assay Standardization and Harmonization Examples

PDL-1 IHC Comparability Example

An example of a collaboration that addresses comparability of assay approaches across multiple immunohistochemistry (IHC)-based PD-L1 tests is the Blueprint PD-L1 IHC Assay Comparison Project developed by four pharmaceutical companies (Bristol-Myers Squibb, Merck & Co. Inc., AstraZeneca PLC, and Genentech, Inc.) and two diagnostic companies (Agilent Technologies, Inc./Dako Corp and Roche/ Ventana Medical Systems, Inc.) in collaboration with the International Association for the Study of Lung Cancer and the American Association for Cancer Research (AACR). The project aims to cross compare four different diagnostics, including U.S. Food and Drug Administration (FDA)-approved tests, for detection of PD-L1 expression in tumor tissue (Averbuch et al., 2015). The PD-L1 IHC 22C3 pharmDx test was approved as a companion diagnostic to pembrolizumab as a single agent in second-line nonsmall-cell lung cancer (NSCLC). The test was used to determine patient eligibility in a single arm study KEYNOTE 001. The PD-L1 IHC 28-8 pharmDx test was approved by the FDA as a complementary test to another PD-1 inhibitor, nivolumab, in the nonsquamous nonsmall-cell lung cancer (NSCLC) and melanoma patient populations. The scope of the Blueprint Project was to establish technical comparability between the assays. Preliminary results of this effort were presented at the 2016 AACR annual meeting. Analyses from the Blueprint Project confirm that there is high concordance for the two approved PD-L1 diagnostics in NSCLC (American Association for Cancer Research, 2016; Hirsch et al., 2017).

Assay Harmonization Effort Examples

Currently, there are several ongoing initiatives to coordinate and harmonize immunoprofiling efforts including the Human Immunology Project, Minimal Information About T Cell Assays (MIATA), human leukocyte antigen-peptide multimer assays, and others (Britten et al., 2009; Britten et al., 2012; Maecker et al., 2010; Maecker, McCoy, & Nussenblatt, 2012; Mandruzzato et al., 2016).

Other technologies, such as gene expression microarrays, have achieved a reasonable degree of standardization led by consortia such as the Microarray Quality Control (Patterson et al., 2006), the External RNA Controls Consortium (Devonshire, Elaswarapu, & Foy, 2010), and the EMERALD project (Beisvåg et al., 2011).

Another example of assay harmonization to minimize data variability and allow worldwide correlations is the Immunoscore initiative (Galon et al., 2012). Effective large-scale assay harmonization efforts have been conducted for IHC-based immunological assays of immune cell populations in formalin-fixed paraffin-embedded (FFPE) tumor sections. The Immunoscore includes the immune cell density, calculated by numerical quantification of two lymphocyte populations, cytotoxic and memory T cells at the tumor center, and the invasive margin of tumors. This criterion has the potential to establish prognosis of patient clinical outcome,

regardless of the absence of other cancer-associated prognostic markers, such as in early tumor stage (I/II) patients. Importantly, it will need to be validated as a predictor of response for immunotherapy.

Pre-analytical Considerations for Standardization of Key Assays

Pre-analytical processing of samples for diagnostic assays including those used for single-cell immune response assays, such as ELISpot or flow cytometric analysis, includes patient-related factors such as tissue-ischemia time, pretreatment with drugs, dynamic nature of the analyte, and sample heterogeneity. Analyte stability can be affected by the sample collection process including anticoagulants and preservatives used for blood draws, freezing/thawing conditions, time between collection and testing, and storage conditions before processing (Mallone et al., 2011).

IHC, the most widely used platform for biomarker assessment in diagnostic surgical pathology and for retrospective research, is a multistep process that requires standardized conditions for tissue collection, fixation and processing, preparation of the IHC slide, and interpretation of the staining results. IHC-based assays remain important tests as complementary diagnostics and companion diagnostics to assess antigen expression on diagnostic or surgical specimens for selecting patients for specific targeted therapies (e.g., HER2 expression for Herceptin), and more recently PD-L1 measurement as a companion diagnostic for pembrolizumab treatment of NSCLC patients. Published guidelines for measuring established biomarkers such as estrogen receptor, progesterone receptor, and HER2 are available (Hammond et al., 2010). General guidelines, including analyte stability and laboratory quality control, for performing analysis of tissue-based molecular biomarkers have been published (Cree et al., 2014).

Next-generation sequencing tests for tumor mutation analysis, similar to other complex molecular diagnostic tests, should demonstrate adequate analytical performance. It should follow standard operating procedures that specifically address materials and procedures including patient's sample type, method of nucleic acid extraction, as well as technical metrics for nucleic acid quantification and quality, which can negatively impact on sensitivity and reproducibility of the assay (Pant, Weiner, & Marton, 2014; Rehm et al., 2013).

The preparation of intact and pure mRNA is one of the key factors in mRNA gene quantification using gene expression profiling of RNA sequencing. Extraction of nucleic acids and particularly RNA is very sensitive to nucleases. Thus, nuclease free conditions should be implemented to control variability in steps such as sample collection, tissue fixation, and FFPE block handling including sectioning. For the extraction of nucleic acids from the FFPE tumor tissue, a method for the simultaneous isolation of high-quality DNA, RNA, and microRNA as well as protein from the same sample has been developed (Kalmar et al., 2013).

Appendix 3: The PACT Design Team

| INDUSTRY PARTICIPANTS | Jeff Engelman (Novartis)—Industry Co-Chair | | Axel Hoos (GSK)—Industry Co-Chair | |
|-------------------------|--|-----------------------------|-----------------------------------|----------------------------|
| | Bob Abraham (Pfizer) | Matthew Albert (Genentech) | Carl Barrett (AstraZeneca) | Olaf Christensen (EMD) |
| | Ute Dugan (BMS) | Jeff Ecsedy (Takeda) | Jessie English (EMD) | Howard Fingert (Takeda) |
| | Vicki Goodman (BMS) | Thomas J. Hudson (AbbVie) | Norbert Kraut (B-I) | Stuart Lutzker (Genentech) |
| | Greg Plowman (Lilly) | Chandra Ramanathan (Bayer) | David Reese (Amgen) | Paul Rejto (Pfizer) |
| | Andrew Schade (Lilly) | Armin Schuler (EMD) | Flavio Solca (B-I) | Jianda Yuan (Merck) |
| GOVERNMENT PARTICIPANTS | Helen Chen (NCI)—NIH Co-Chair | | Percy Ivy (NCI)—NIH Co-Chair | |
| | Rebecca Baker (NIH) | Gideon Blumenthal (FDA) | Kevin Howcroft (NCI) | Tony Kerlavage (NCI) |
| | Allison Lea (NIH) | Ke Liu (FDA) | Lisa McShane (NCI) | Reena Phillip (FDA) |
| | Larry Rubenstein (NCI) | Malcolm Smith (NCI) | Howard Streicher (NCI) | Marc Theoret (FDA) |
| | Magdalene Thurin (NCI) | | | |
| ACADEMIC PARTICIPANTS | John Byrd (OSU) | Levi Garraway (Broad/Lilly) | Steve Hodi (DFCI) | Patricia LoRusso (Yale) |
| | Antoni Ribas (UCLA) | Lillian Siu (PMCC) | Mario Sznol (Yale) | Jedd Wolchok (MSKCC) |
| PACT PROGRAM MANAGEMENT | Stacey Adam (FNIH) | David Wholley (FNIH) | | |

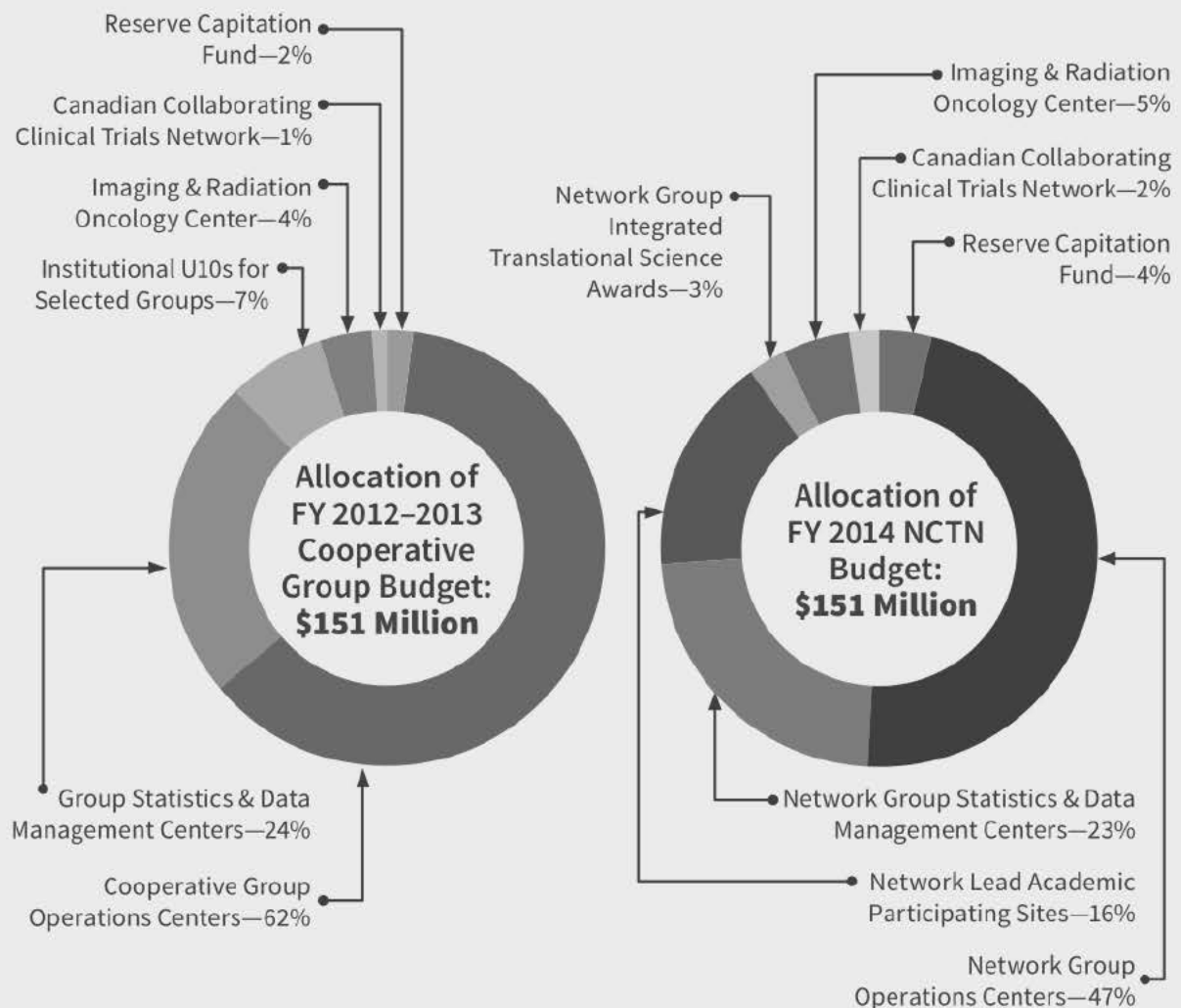
Appendix 4: Detailed Description of the Cancer Therapy Evaluation Program (CTEP) – National Clinical Trials Network (NCTN)

The NCTN Budget

The overall NCTN budget for these awards is \$151 million. This amount is the same as the total budget provided to the Cooperative Groups for awards in each of fiscal years (FY) 2012 and 2013, despite the substantial reductions in the National Cancer Institute (NCI) budget that resulted from sequestration starting in 2013. What has changed, however, is the distribution of funds to the various components of the NCTN, as compared with the components of the former Cooperative Group program.

The distribution of funds to the Network Group Operations Center grants changed from 62 percent in FY 2012 and 2013 to 47 percent in FY 2014 due to the consolidation of the infrastructures of the Operations and Statistical Centers; funding of new components in the NCTN, including the Lead Academic Participating Sites and Integrated Translational Science Awards; and expansion of the Imaging and Radiology Oncology Group for the entire network. The new system provides for an annual enrollment of about 17,000 patients on interventional trials, a 15 percent reduction compared with about 21,000 enrolled patients in recent years. This reduction is anticipated to occur gradually over 2 to 3 years. To this end, NCI reserved funds to distribute to the NCTN groups later in FY 2014 to accommodate an enrollment of about 21,000 patients.

COMPARISON OF COOPERATIVE GROUP PROGRAM FUNDING AND NCTN PROGRAM FUNDING



Funding Precision Medicine Trials

NCI believes that reducing the budget of the Network Group Operations Centers will not impede the NCTN's ability to perform important trials. Conducting the new generation of clinical trials requires new technologies and procedures, including tissue collection (fresh biopsy samples are often necessary), advanced DNA and RNA sequencing methods with rapid turnaround times, and complex analytic algorithms to distinguish normal genetic variants from tumor-specific changes. These, in turn, entail new expenses for surgery, interventional radiology, molecular pathology, and bioinformatics that have not typically been a part of clinical trials.

However, although the screening tests may need to be performed on very large numbers of patients to find those whose tumors exhibit the appropriate molecular profile, the numbers of patients required for interventional studies are likely to be smaller than what was required in previous trials.

That is because the patient selection is based on having the target for the new therapy, leading to larger differences in clinical benefit (such as how long patients live overall or live without tumor progression) between the intervention and control groups. Thus, future clinical trials will, in many cases, require fewer numbers of patients due to the selection of patients most likely to benefit from the intervention being tested.

Although screening patients for tumors with specific molecular characteristics may require large numbers of patients, the screening components of studies are less costly than the actual interventional study. Hence, clinical trials in the future are likely to involve screening components, which will be reimbursed at a lower rate, with smaller interventional components that will be reimbursed at higher rates. More precision in patient selection will permit study designs that can aim for larger therapeutic effects and thereby further decrease the size of trials.

Efficiencies in Collaboration

These changes will, however, require the NCTN groups to function differently compared with how they functioned in the previous system. For example, NCTN groups should be able to reduce the costs of conducting trials by sharing resources. If a particular group has many active trials, it may have to decrease the number of new trials it is planning. Groups with fewer active trials can take up those new trials instead. This collaborative approach should allow members of one NCTN group to support trials led by other groups and should afford NCTN members an ability to conduct a full portfolio of trials in the most common cancers.

Because the NCTN has only four U.S. adult groups, with fewer Operations and Statistical Centers that require financial support, some savings are anticipated. This consolidation was planned for over the past several years, and NCI provided \$24 million in funding supplements to the newly consolidated groups to help them absorb the costs of their ongoing trials as well as to fund the integration of their separate infrastructures.

NCI also provided more than \$40 million in other funding supplements to transition all the groups to a common data management system (Medidata Rave®), develop an integrated IT system for the tissue banks, and implement specific precision medicine clinical trials.

Additional Support

For the past several years, NCI has provided significant additional annual support for the Cooperative Groups and will continue to provide these funds for the NCTN, in addition to the grant funding described above. Clinical trials are complex undertakings that require a host of support organizations and funding streams. The new system includes a number of other features that are not included in the NCTN awards but are essential to carrying out the NCTN mission.

The additional support includes:

- Central Institutional Review Boards, an important component of NCI's clinical trials system that has added speed, efficiency, and uniformity to ethics review.

- ▶ The Cancer Trials Support Unit, an NCI-funded contract that provides clinical investigators and their staff with one-stop online access to NCTN trials and allows investigators to register new patients.
- ▶ A dedicated tissue bank for each Network group funded through a separate NCI award mechanism.
- ▶ The Biomarker, Imaging, and Quality of Life Studies Funding Program, a separate funding stream for NCTN trials that supports correlative science studies on group trials. NCTN groups compete for funds that are specifically reserved annually for this purpose. The availability of dedicated funds greatly facilitates coordination as clinical trials must meet stringent deadlines.
- ▶ In addition, approximately one-quarter of patient accrual on NCTN treatment trials is paid for by the NCI Community Oncology Research Program (NCORP; previously the Community Clinical Oncology Program/Minority-Based Community Clinical Oncology Program). The community hospitals and medical centers participating in the NCORP are reimbursed for accruing patients to NCTN treatment trials by their NCORP awards, not via the NCTN Group Operations award.

| ADDITIONAL ANNUAL NCI SUPPORT | |
|---|------------------------|
| NCI Central IRBs (Adult & Pediatrics) | \$4.5 Million |
| Cancer Trials Support Unit | \$14.0 |
| Tissue Banks | \$8.6 |
| Biomarker, Imaging, and Quality of Life Studies Funding Program | \$10.0 |
| NCORP Support for NCTN Treatment Trials (Estimated) | \$33.1 |
| | \$70.2 Million* |

Other NCI support includes but is not limited to:

- ▶ Operations of common data management system (Medidata Rave®)
- ▶ Clinical trials auditing
- ▶ Drug storage and distribution
- ▶ Regulatory oversight (CTEP IND Studies)

*This is an approximation and is dependent on annual NCI appropriations.

Finally, in addition to these substantial annual expenditures, NCI also subsidizes the NCTN by paying for many other essential clinical trial functions, thereby further reducing costs borne by the Network groups:

- ▶ NCI will pay for the licenses and hosting fees of the electronic, common data management system, called Medidata Rave®, used by all NCTN groups.
- ▶ NCI will oversee a national audit system for NCTN trials.
- ▶ NCI will manage Investigational New Drug applications to the U.S. Food and Drug Administration along with the distribution of these drugs for many NCTN trials.

It is estimated that support for these activities costs NCI approximately \$15 million annually.

<https://www.cancer.gov/research/areas/clinical-trials/nctn/budget>

Appendix 5: Active NIH/NCI Requests for Applications (RFAs) Relevant to PACT

2017

1. CA17-009 Mechanisms of Cancer Drug Resistance and Sensitivity (U54)
2. CA17-006 Cancer Immunologic Data Commons (CIDC) (U24)
3. CA17-005 Cancer Immune Monitoring and Analysis Centers (U24)
4. CA17-013 Advanced Development and Validation of Emerging Biospecimen Science Technologies for Basic and Clinical Cancer Research (R33)

2016

5. CA16-501 Limited Competition: Cancer Immunotherapy Trials Network (CITN)(UM1)

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From: Wholley, David (FNIH) [T]
Sent: Tue, 10 Oct 2017 20:00:15 +0000
To: Baker, Rebecca (NIH/OD) [E]; Wolinetz, Carrie (NIH/OD) [E]
Cc: Collins, Francis (NIH/OD) [E]; Tabak, Lawrence (NIH/OD) [E]
Subject: FW: Partnership for Accelerating Cancer Therapies (PACT)

FYI I asked for a formal email of commitment from Gilead. Here it is.

David Wholley
Director, Research Partnerships
Foundation for the National Institutes of Health
(301) 594-6343
fnih.org

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-----Original Message-----

From: Kacy Hutchison [<mailto:Kacy.Hutchison@gilead.com>]
Sent: Tuesday, October 10, 2017 3:24 PM
To: Wholley, David (FNIH) [T] <dwholley@fnih.org>
Cc: Wolf-Rodda, Julie (FNIH) [T] <jwolf-rodde@fnih.org>; Adam, Stacey (FNIH) [T] <sadam@fnih.org>; Gregg Alton <Gregg.Alton@gilead.com>; Amy Flood <Amy.Flood@gilead.com>; Chuck Clapton <Chuck.Clapton@gilead.com>
Subject: RE: Partnership for Accelerating Cancer Therapies (PACT)

Hi David -

Thank you for the call today. On behalf of Gilead Sciences, we are pleased to support the NIH Foundation and your invitation to join the Partnership for Accelerating Cancer Therapies (PACT). Per your request of industry partners, (b) (4), (b) (5) as a multi-year contribution as part of your public/private collaboration to help fund the development of standardized biomarkers and assays for trials of new cancer immunotherapies and combination therapies.

We look forward to future discussions. I'll be back in touch in regard to the information you requested in preparation for the announcement on Thursday shortly.

Sincerely,

Kacy

Kacy Hutchison
Vice President, North America Government Affairs Gilead Sciences, Inc.
333 Lakeside Drive,
Foster City, CA 94404
(O) 650-522-1831
(C) (b) (6)

-----Original Message-----

From: Wholley, David (FNIH) [T] [<mailto:dwholley@fnih.org>]

Sent: Tuesday, October 10, 2017 1:07 PM
To: Kacy Hutchison; Adam, Stacey (FNIH) [T]
Cc: Wolf-Rodda, Julie (FNIH) [T]
Subject: RE: Partnership for Accelerating Cancer Therapies (PACT)

Stacey, can you please send Kacy a template (b) (4) Thanks

David Wholley
Director, Research Partnerships
Foundation for the National Institutes of Health
(301) 594-6343
fnih.org

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From: Wholley, David (FNIH) [T]
Sent: Wed, 25 Oct 2017 19:19:14 +0000
To: Collins, Francis (NIH/OD) [E]; Doroshov, James (NIH/NCI) [E]; Lowy, Douglas (NIH/NCI) [E]; Tabak, Lawrence (NIH/OD) [E]; Baker, Rebecca (NIH/OD) [E]; Wolinetz, Carrie (NIH/OD) [E]
Cc: Adam, Stacey (FNIH) [T]
Subject: FW: Partnership for Accelerating Cancer Therapies (PACT)
Attachments: (b) (4)

FYI. Perhaps we can discuss this tomorrow.

-----Original Message-----

From: Chuck Clapton [mailto:Chuck.Clapton@gilead.com]
Sent: Wednesday, October 25, 2017 10:58 AM
To: Wholley, David (FNIH) [T] <dwholley@fnihi.org>
Subject: RE: Partnership for Accelerating Cancer Therapies (PACT)

David,

Thanks again for speaking last week

(b) (4)

(b) (4)

(b) (4) and I would be grateful for any assistance you can provide in helping us navigate this process. Thanks again for all of your assistance.

Chuck

-----Original Message-----

From: Wholley, David (FNIH) [T] [mailto:dwholley@fnihi.org]
Sent: Wednesday, October 18, 2017 9:30 AM
To: Chuck Clapton
Subject: Re: Partnership for Accelerating Cancer Therapies (PACT)

It may need to be this afternoon but I will call.

Sent from my BlackBerry 10 smartphone.

Original Message

From: Chuck Clapton
Sent: Wednesday, October 18, 2017 8:58 AM
To: Wholley, David (FNIH) [T]
Subject: RE: Partnership for Accelerating Cancer Therapies (PACT)

David -- thanks for getting back to me. You can call any time it would be convenient for you -- my cell is (b) (6)
(b) (6) Thanks

-----Original Message-----

From: Wholley, David (FNIH) [T] [mailto:dwholley@fnihi.org]
Sent: Tuesday, October 17, 2017 12:13 PM
To: Chuck Clapton
Cc: Adam, Stacey (FNIH) [T]; Melencio, Cheryl (FNIH) [T]
Subject: RE: Partnership for Accelerating Cancer Therapies (PACT)

Sure, Chuck, please let me know when you'd like to speak and number at which you can be reached.

David Wholley
Director, Research Partnerships
Foundation for the National Institutes of Health
(301) 594-6343
fnihi.org

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-----Original Message-----

From: Chuck Clapton [<mailto:Chuck.Clapton@gilead.com>]
Sent: Tuesday, October 17, 2017 9:59 AM
To: Wholley, David (FNIH) [T] <dwholley@fnihi.org>
Subject: RE: Partnership for Accelerating Cancer Therapies (PACT)

David,
Is there any chance you might be around anytime today for a call? Just want to follow up on a couple of questions on exec comm and joint steering committee. Thanks Chuck

Direct (b) (6) cell (b) (6)

-----Original Message-----

From: Wholley, David (FNIH) [T] [<mailto:dwholley@fnihi.org>]
Sent: Tuesday, October 10, 2017 11:45 AM
To: Chuck Clapton
Subject: Re: Partnership for Accelerating Cancer Therapies (PACT)

Can you speak now? If not I should be available again in 30 minutes.

Sent from my BlackBerry 10 smartphone.

Original Message

From: Wholley, David (FNIH) [T]
Sent: Tuesday, October 10, 2017 11:23 AM
To: Chuck Clapton
Subject: RE: Partnership for Accelerating Cancer Therapies (PACT)

Yes, I should be jumping off the train in Union Station within the next 15-20 minutes and can give you a call from my cell. What number should I use to reach you?

David Wholley
Director, Research Partnerships
Foundation for the National Institutes of Health
(301) 594-6343
fnihi.org

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-----Original Message-----

From: Chuck Clapton [<mailto:Chuck.Clapton@gilead.com>]
Sent: Tuesday, October 10, 2017 11:01 AM
To: Wholley, David (FNIH) [T] <dwholley@fnihi.org>
Subject: Re: Partnership for Accelerating Cancer Therapies (PACT)

David,
Do you have any time within the next hour for a quick call? Thanks Chuck

Sent from my iPhone

On Oct 10, 2017, at 8:21 AM, Wholley, David (FNIH) [T] <dwholley@fnihi.org<mailto:dwholley@fnihi.org>> wrote:

Hi Chuck, just checking in to see if there has been any update.
Let me know if we can be of any help.

Sent from my BlackBerry 10 smartphone.
From: Chuck Clapton
Sent: Friday, October 6, 2017 11:05 AM
To: Wholley, David (FNIH) [T]
Cc: Melencio, Cheryl (FNIH) [T]
Subject: RE: Partnership for Accelerating Cancer Therapies (PACT)

Thanks David. I've sent this around to a group of our senior execs and will get back to you asap.

From: Wholley, David (FNIH) [T] [<mailto:dwholley@fnihi.org>]
Sent: Thursday, October 05, 2017 11:20 AM
To: Chuck Clapton
Cc: Melencio, Cheryl (FNIH) [T]
Subject: FW: Partnership for Accelerating Cancer Therapies (PACT)

Chuck - great to meet you last night, and thank you for your offer to help with communicating to John Milligan regarding PACT. Below is the email that our Board Chairman, Steve Paul, had our assistant send to John on his behalf. Please let me know if I can be of any further assistance.

David

David Wholley
Director, Research Partnerships
Foundation for the National Institutes of Health
(301) 594-6343
fnihi.org<www.fnihi.org>

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From: Melencio, Cheryl (FNIH) [T]
Sent: Tuesday, October 03, 2017 11:55 AM
To: John.Milligan@gilead.com<mailto:John.Milligan@gilead.com>
Cc: Steven Paul <steve@thirdrockventures.com<mailto:steve@thirdrockventures.com>>; Wholley, David (FNIH) [T] <dwholley@fnihi.org<mailto:dwholley@fnihi.org>>
Subject: Partnership for Accelerating Cancer Therapies (PACT)

Dear Dr. Milligan:

On behalf of Dr. Steven Paul, Chairman of the Board, Foundation for the National Institutes of Health, please find attached letter.

Thank you.

Cheryl Melencio

Cheryl Melencio
Executive Assistant, Research Partnerships Foundation for the National Institutes of Health

(301) 402-4970
fnihi.org<www.fnihi.org>

The FNIH is the #1 ranked biomedical research organization & earned a 4-star rating from Charity Navigator<<https://www.charitynavigator.org/index.cfm?bay=search.summary&orgid=6244>>.

